ARCHIVES OF DISEASE IN CHILDHOOD.

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THE BONE CHANGES OCCURRING IN RENAL AND COELIAC INFANTILISM, AND THEIR RELATIONSHIP TO RICKETS

PART I. RENAL RICKETS.

BY

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The occurrence of bone deformities associated with the presence of albumin in the urine was first observed by R. C. Lucas (1) who in the year 1883 published a paper entitled "A Form of Late Rickets associated with Albuminuria." A perusal of this paper, however, shows that the cases described were not examples of renal infantilism. The interest of British paediatricians in renal infantilism was first aroused by Morley Fletcher (2) who in the year 1911 showed before the Children's Section of the Royal Society of Medicine, a typical example of this condition occurring in a child who had developed genu valgum when five years of age. In a paper written by Miller and myself (3) in 1912 the occurrence of genu valgum in several of the cases was commented on. Naish (4) writing upon this subject in the same year said: "The presence of rickets usually of late origin in as many as five out of the eight cases is a striking phenomenon," but the credit for emphasising the importance and striking character of the bone changes is clearly due to Barber (5) who has published a series of papers on renal dwarfism, and to whose description of the bone changes there is, from a purely clinical standpoint, little to add. Barber regards the bone changes as typical of late rickets, but has not attempted any explanation of the reason why this should occur. Paterson (6) writing in 1920 discusses whether the bone changes should be regarded as those of rickets or not, and infers that in his view the condition is not rickets, but "would suggest that these bony changes are nutritional in origin." Shipley, Park, McCollum and Simmonds (7) recording their observations on one case, suggest that the condition may be a true renal rickets, whereas Lathrop (8) from the same medical school, in a paper recently published, states that although the clinical appearances are difficult to differentiate from rickets, the radiogram shows nothing suggestive of that disease, and the blood calcium and phosphorus are distinctly outside the rachitic zone.

I have recently had the opportunity of investigating somewhat fully the clinical characteristics, and the chemical and radiographic findings of five hitherto unpublished cases of renal infantilism with bone changes. These cases form the basis of the present communication in which an attempt is made to classify the bone changes and to explain their pathogenesis.

Clinical Description.

The clinical characteristics of renal infantilism, or dwarfism, are now so well known that, in a paper which concerns itself chiefly with the bone deformities, a lengthy description of the disease is not called for. It may, however, be advantageous to recall the salient points in its symptomatology. The children are always stunted in growth and there is a delay in the appearance of secondary sex characteristics. Apart from the retardation of development the most characteristic symptoms are polydipsia and polyuria, often of extreme degree and associated with nocturnal incontinence. The facies is frequently a typical one, being sallow in colour and characteristically wrinkled. The urine has a low specific gravity and usually contains a faint haze of albumin. Cardiovascular changes may be, but usually are not, present. The age at the onset of the symptoms varies. In quite a considerable proportion the symptoms appear to have been present from birth, whereas in others the child was apparently normal for the first few years of life. The disease is a fatal one, death occurring from uræmia, usually in the second decade of life.

The autopsy findings have in the great majority of cases shown very small kidneys the result of severe chronic interstitial nephritis, but cases are on record associated with pyelitis and apparently an ascending infection of the urinary tract, congenital cystic kidneys and bilateral renal calculi. The end result is, however, identical in all cases, *i.e.*, an almost complete destruction of the renal parenchyma.

Those cases in which bone deformities occur are now usually designated "renal rickets." Genu valgum, which may develop very rapidly, is the commonest manifestation of renal as of coeliac rickets. Enlargement of the epiphyses of the wrists and ankles may occur with or without genu valgum. In some instances bowing of the legs occurs, instead of genu valgum, and in others again the picture is that of severe rickets with well marked rosary, Harrison's sulcus, pigeon chest, enlargement of epiphyses, genu valgum, etc.

The most striking deformities that I have seen are those present in H.T., of whom a photograph is shown (Fig. 1). This boy is seventeen years of age, has a very marked rosary, a deformed chest, enlargement of the epiphyses, and extraordinary bending of the femora, tibiæ and fibulæ. In some cases there does not appear to be any bending of the shafts of the long bones, but the epiphyses are enlarged, and there is obvious bending or displacement of the enlarged epiphyseal end of the bone, the explanation of which will appear later on in this paper.

The ages of the children at the onset of the bone changes varies considerably. Barber states that the usual time for genu valgum to develop is between eleven and fourteen years of age. The earliest age at which I have seen bone changes is sixteen months. Paterson has described a case at twenty-one months, and also one in which, according to the parents' history, the deformities were present at birth [9]. On the other hand there are cases on record in which the bone deformities have not been recognised until the age of seventeen years. In my cases the onset has been earlier, all having occurred before the age of ten years, the usual time of onset being from five to seven years.

Fig. 1.—Photograph of H.T., aged 16 years, showing the severe nature of the deformities which may occur in renal rickets.

Fig 2.—Radiogram (H.L.) showing atrophic type of renal rickets. Note the thin cortex, well marked rickets at the epiphyseal line, fracture of the shaft of the ulna, and general fragile atrophic and osteoporotic character of the bones

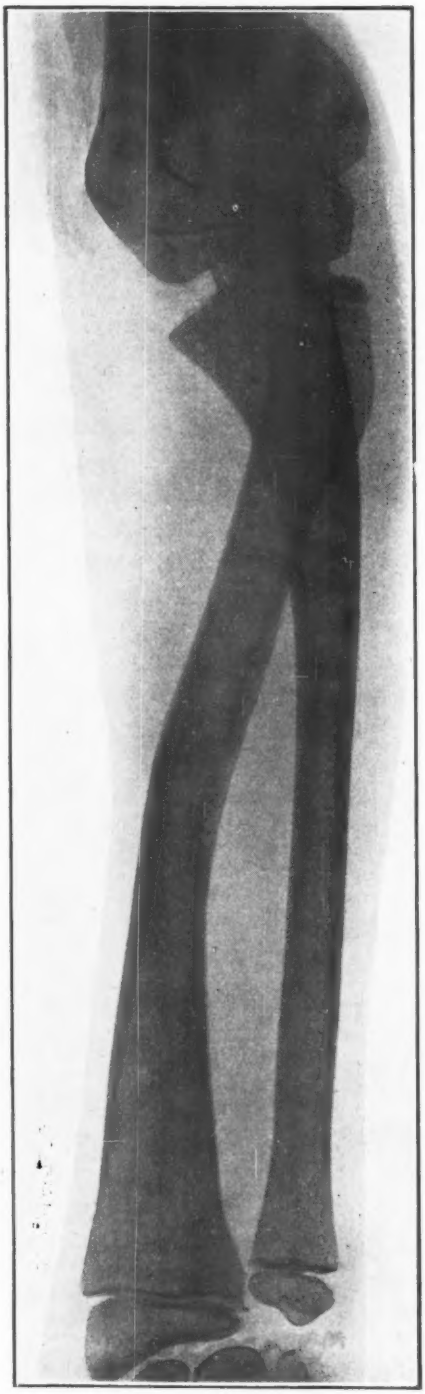


Fig. 3.—Radiogram from the same case as Fig. 2, taken five and a half years later. The bone is still somewhat fragile and atrophic but the rickets has completely healed. Transverse striations are well seen at the lower end of the radius.

Radiographic Manifestations.

A study of radiograms of renal rickets shows that the bone changes fall into three well defined groups, which I propose to call :—

1. The atrophic type.
2. The florid type.
3. The woolly, stippled, or honeycomb type.

1. *The Atrophic Type.*

In this group the radiogram (Fig. 2) presents a picture strikingly similar to that seen in coeliac rickets of a moderate degree. The whole bone presents a fragile, atrophic, osteoporotic appearance. Near the epiphyseal end of the diaphysis there may be seen one or two straight lines of cancellous tissue, running parallel to the epiphyseal line. The cortex is also thin and atrophic. A fracture, or fractures of the shaft may be present, but these are not so commonly seen as in coeliac disease, and finally there is well marked rickets at the epiphyseal line.

2. *The Florid Type.*

The appearances in this group are those characteristic of florid rickets. The shaft may perhaps be a little more fragile than that of a normal child of the same development, but not sufficiently so to call for comment, whilst the changes so characteristic of the atrophic type are absent. (Figs. 4, 5, 6, 9, 10.)

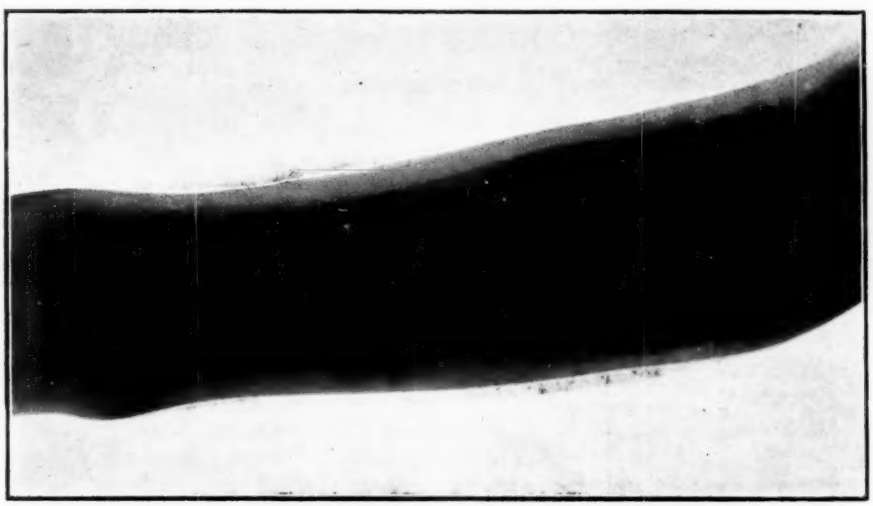
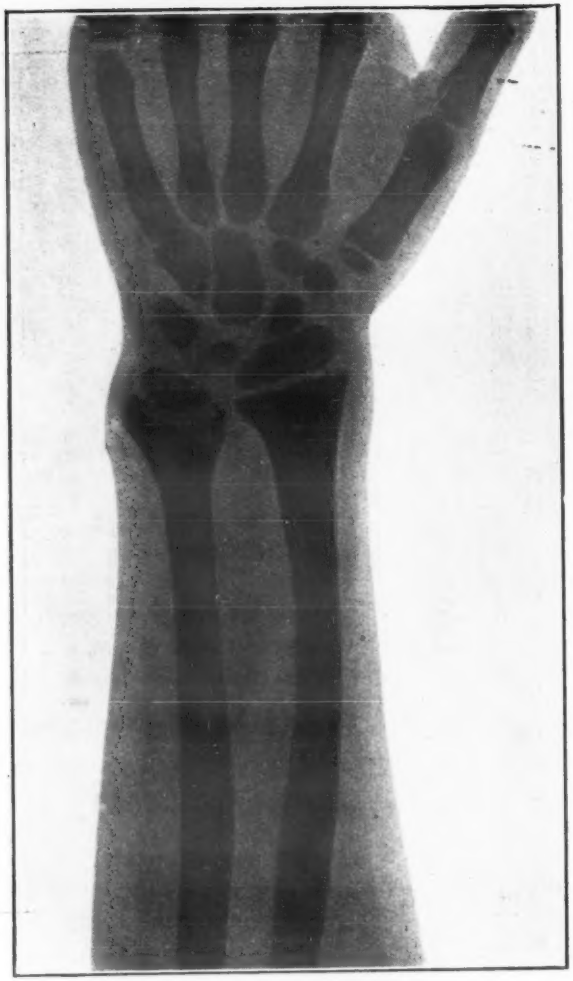


Fig. 4.—Radiogram of N.H., taken Jan. 30th, 1926, showing florid type of renal rickets.

3. *The Woolly, Stippled, or Honeycomb Type.*

This is the most extraordinary manifestation of renal rickets. It is quite unlike the picture usually associated with rickets, and yet is so characteristic that a radiographer who has had experience of these cases can make the diagnosis of renal rickets from the radiogram. (Figs. 11, 12, 14, 15.) In this type the



Figs. 5, 6, 7—Radiograms of N.H., taken on the following dates:—23/3/26, 11/5/26, 23/6/26, showing stages in the complete cure of rickets.

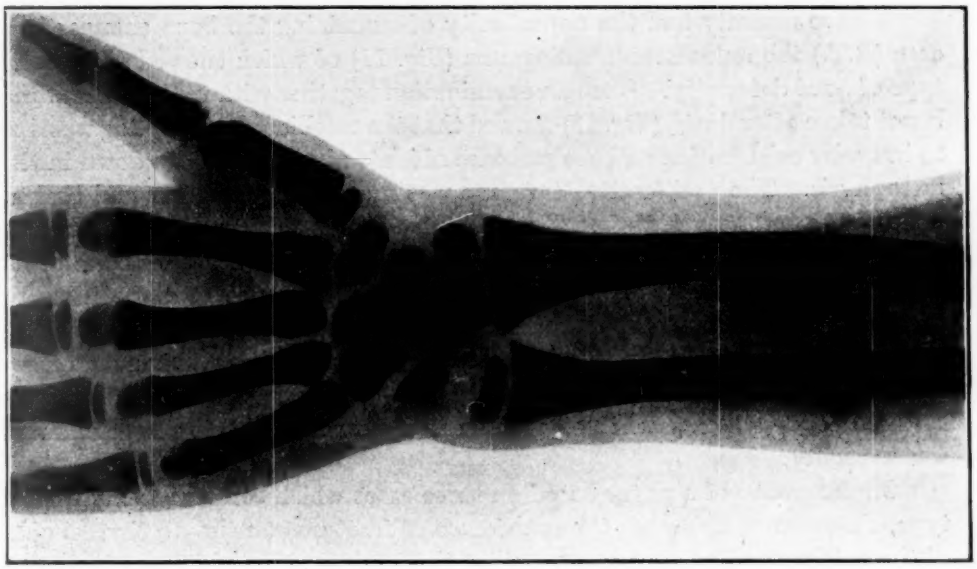


Fig. 8. Radiogram of N.H., taken on 30/8/26, showing stage in the complete cure of rickets.

epiphyseal end of the shaft of the bone is swollen, forming a large metaphysis. This portion of the bone presents a curious appearance which sometimes suggests a honeycomb, at other times shows marked stippling, whilst at others it has a woolly appearance, the bone looking moth-eaten as if the shaft were being eaten away subperiostally and giving at first sight the suggestion of osteomyelitis or syphilitic disease. The metaphysis extends over a much greater area than in ordinary rickets. Associated with these appearances is a degree of osteoporosis throughout the shaft of the bone, but the cortex does not appear thin as in the atrophic type. The condition of the shaft in the atrophic type is one which suggests that the bone has never been anything else but atrophic, whereas in the woolly type it is conceivable that osteoporosis has occurred in a bone which at some previous time might have approached the normal.

The bones of the vault of the skull sometimes show changes and in the case of H.T., these are most marked. (Fig. 16). These bones are greatly thickened and show extreme stippling presenting an appearance in the radiogram quite unlike anything with which I am acquainted with the exception of Paget's disease. Indeed my colleague, Dr. Teall reported on this case as follows :— " the bone change in the skull is, from the radiographic point of view, identical with that of Paget's disease."

The changes do not occur to the same degree in all the long bones, e.g., the radius and ulna of one arm may show changes much more marked than those of the other side. Thus the metaphysis on one side may be larger and show more stippling, whereas on the other, it may show a more eroded appearance and not so much enlargement. (Fig. 14).

I have recently had the opportunity of examining the bone changes in a case (B.T.) the antemortem radiograms (Fig. 11) of which showed the woolly type of bone deformity. Such an examination together with radiograms of the bones taken after death (Fig. 12) showed that the woolliness or stippling was due to irregular calcification and the presence of islets of cartilage deep down in the metaphysis. The proliferative cartilage was much more irregular and broken up than in ordinary rickets. The metaphysis was deeper, and although it showed broadening or splaying out, the degree of broadening was not so great as in uncomplicated rickets. As a result of the presence of these islets of cartilage deep in the metaphysis (Fig. 13), the whole metaphysis was bent on the diaphysis and this, together with bending of the shaft as a result of osteoporosis in the neighbourhood of the wrists and ankles, resulted in a deformity at these points which gave the epiphysis an appearance of being larger than it was in reality.

In the course of a paper based on three cases which conform to my woolly type, Paterson [6] describes the occurrence of fractures on the diaphyseal side of the epiphyseal line, and suggests that the " stippled " appearance is due to the throwing out of callus in an attempt to repair such fractures. Whilst the occurrence of fractures in this situation is obviously possible owing to the softness of the tissue, yet up to the present time I have not observed them in any of my cases and the stippling is due, as already explained, to the irregularity of calcification in the metaphysis. In a description of a case of renal infantilism with bone changes of the woolly type, Shipley [7] pointed out that the changes in the bones revealed by X-ray and histology were most extensive and differed from the changes ordinarily found in rickets. " The proliferative cartilage was most irregular and the calcification defective. In the deep metaphysis were large islands of cartilage bordered on one or more sides by dense calcium deposits. These islands of cartilage gave to the metaphysis as seen in the Röentgenogram a honeycomb appearance. The trabeculæ were thin, and the osteoid borders comparatively speaking narrow. Surrounding the trabeculæ and islands of cartilage, and lying between them, was a loose fibrous tissue. Obviously for a long time the pathological condition in the bone had been in a state of flux between healing and relapse." They have suggested the possibility that this condition may have " its origin in the extreme functional disability of the kidney properly to excrete phosphate," and that if this suggestion " should prove to be correct a true renal rickets exists, and rickets under certain conditions, may have an endogenous origin." I believe this suggestion to be correct. As evidence against the rachitic origin of the bone deformity Paterson mentions the absence of bowing of the bones in one of his cases, a child aged twenty months, but as I have already pointed out, extreme bending of the bones does occur in the woolly type. He also thinks that the histological changes in the bone are not those of rickets, but his description of these changes is almost identical with that I have quoted from the paper by Shipley and his co-workers. These investigators, whose experience of experimental rickets is unrivalled, accept the view that the changes are rachitic in nature and that they " may belong to the low calcium form of the disease."

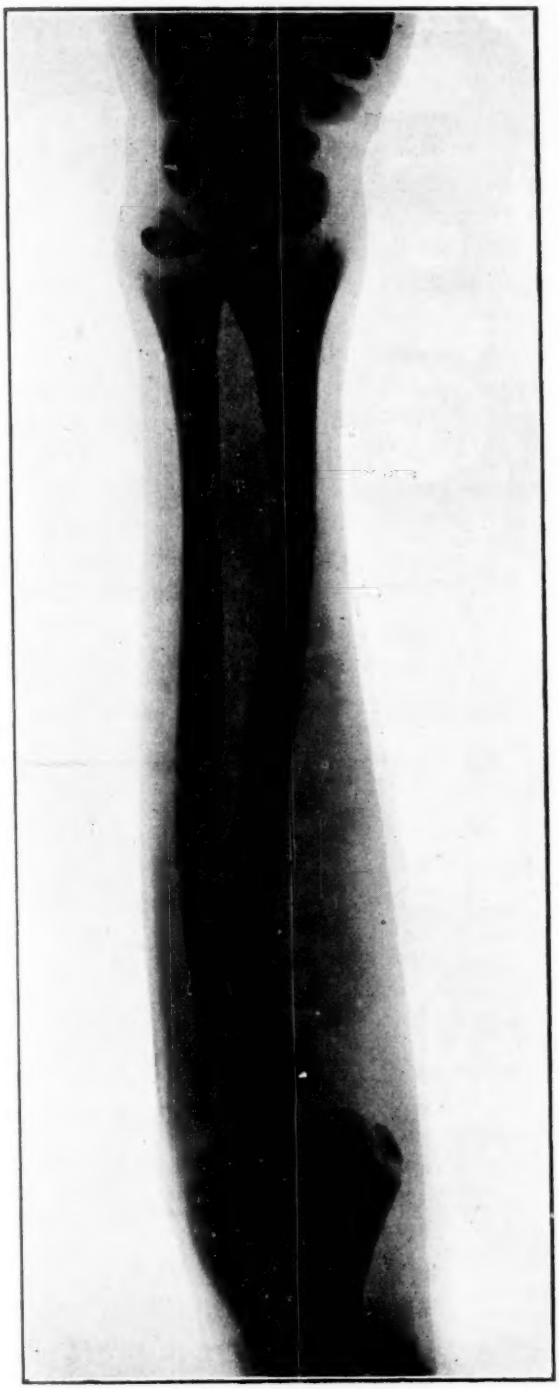


Fig. 9.—Radiogram (L.M.) showing florid type of renal rickets.

Sections of the bone in the case (B.T.) to which I have just referred shows a condition similar to that described by Paterson and by Shipley. I have referred these sections to Professor Haswell Wilson, Professor of Pathology in the University of Birmingham, who considers that although the changes present differ from those ordinarily seen in rickets, yet they are definitely rachitic in nature.

Discussion. There appears no explanation why one case should show florid rickets, another atrophic, and yet another the woolly type, though the last is, I think, the most serious form of the disease. Again, although there seems no reason why the florid should not change into the atrophic type, yet in my experience all three types always breed true, and there is never any changing from one type to another, nor does one long bone show one type of change, and another bone in the same child a change of the other types. The cases reported by Barber appear to have been instances of florid rickets, and he does not seem to be familiar with the atrophic or woolly types.

From a study of my cases two striking, if apparently contradictory results, have emerged. First, that unlike the results obtained in coeliac rickets, ultra-violet irradiation does not produce a cure of renal rickets ; indeed I have obtained considerable evidence showing that it makes the condition worse.

Secondly, that the atrophic and florid types of renal rickets may show complete recovery. Recovery in the atrophic type results in the production of a bone, whose radiogram resembles that seen in mild coeliac disease before the production of rickets, *i.e.*, a somewhat fragile and osteoporotic bone with a thin cortex, showing one or more transverse lines, in the neighbourhood of, and running parallel to the epiphyseal line, the latter being perfectly sharp and straight. The reproduced radiograms of H.L. (Figs. 2 and 3) show the atrophic type of renal rickets, before and after cure, the first radiogram being taken four years ago when he was twelve years of age the second recently. He is now sixteen years of age and his condition is astonishingly good. Recovery in the florid type is well shown in the series of radiograms of N.H., a girl aged ten years. (Figs. 4, 5, 6, 7, 8.) I have not seen any case in which ossification is complete, since none of my cases have lived beyond seventeen years, but in Barber's last paper there are radiograms of a girl aged twenty who had been the subject of florid rickets, but in whom the epiphyses have joined up so that ossification is complete, and as far as can be judged from the reproduction of the radiograms the bone is normal. From the quotation given above from Shipley's paper, it is obvious that even in the woolly type, attempts at healing take place from time to time.

Blood Chemistry in Renal Rickets.

In many instances the serum shows an extreme degree of lipæmia, in one case an estimation showed that the serum contained almost nineteen per cent. of fat. In all cases there is a very high degree of nitrogen retention (azotæmia). The actual figures obtained are set out in tabular form (Table 1), but here it may be stated that in a series of twenty-three estimations on five cases the blood-urea values have varied from 113 mg. to 720 mg. per cent, the latter of course occurring shortly before death. Non-protein nitrogen and creatinin have also been very high. In chronic interstitial or azotæmic nephritis in adults the blood phosphorus is greatly increased, and roughly follows the curve of the blood urea, and this is found to be the case in renal rickets. The values

Fig. 10.—Radiogram taken *post-mortem* of costochrondral junction of rib of L.M., showing the typical appearance of florid rickets.

TABLE I.

Case.	Date.	Urea.	Non-Protein Nitrogen.	Creatinin.	Chlorides.	Calcium.	Inorganic Phosphorus.	Comments.
N.H. ♀ aged 10 years.	26/2/26	117						Florid rickets.
	8/4/26	180				10·0	13·9	
	16/4/26	138·3				11·7	6·0	
	19/5/26	150				9·0	6·1	Rickets healing.
	29/6/26	137	78·0	1·5	485	11·1	5·5	,, ,,
	15/9/26	226·5	115·4	1·3	548	10·3	6·5	Rickets healed, recently recovered from an attack of vomiting (? uræmia).
	1/11/26	178·6				10·09	5·58	
	17/11/26	111·5	79·0	1·63	574	9·12	5·23	
A.N. ♂ aged 16 months.	13/4/26					8·6	7·3	Woolly type rickets. Serum contained 18·97 % of fat.
	17/4/26						9·0	
	23/6/26	109·2	54·1	1·27	554			
	1/7/26	117·4	55	1·5	594	7·7	7·1	
	25/9/26	191·6	96·8	1·7	601	9·5	9·5	
	28/10/26	173·3	85·7	1·5		9·0	6·1	
	23/11/26	208·3	115·2	1·4	643	9·3	7·58	
B.T. ♂ aged 10 years.	14/5/26	339				8·2	14·3	Woolly type rickets. Uræmia.
	19/5/26	407·5			706·9	7·3	10·6	Blood taken a few hours before death.
	27/5/26	720·0	370	7·73	545	7·3	13·7	
H.T. ♂ aged 16 years.	21/9/26	136·5	110	2·0	561	12·7	8·5	Woolly type of rickets. Previously treated by ultra violet light, fall in phosphorus on cessation of this treatment.
	11/9/26	135	105	1·9	561	10·0	4·7	
	26/9/26	113·6	59·4	1·4		10·4	4·1	
	19/10/26	112·9	93·8	1·4		14·6	6·35	*p*H 7·16, *p* product of
	10/1/27	134·7				13·0	10·07	$[Ca^{++}]^3 \times [PO_4^{\equiv}]^2$ is 23.40.
	14/1/27	134·7		1·85	597	12·7		
L.M. ♂ aged 16 years.	30/11/26	673·8		5·9	425·7	3·95	16·3	Florid rickets uræmia—death 2/12/26.

This table gives the details of blood chemistry findings, the values are all expressed as milligrammes per cent.

for serum phosphorus (normal, 5 mg. per cent.) have varied between 4·1 mg. and 16·13 mg. per cent., whereas those for serum calcium (normal, 9-10 mg. per cent.) have varied from 3·95 mg. to 14·6 mg. per cent. The blood calcium of 3·95 mg. per cent. occurred shortly before death, and is by far the lowest figure obtained, the next lowest figure being 7·3 mg. per cent. I would, however, emphasise the fact that in only six out of twenty-one estimations was the calcium under 9·0 mg. per cent., but that in every patient the calcium was low, when compared with the amount of blood phosphorus.

Further evidence in favour of the view that in renal rickets the serum calcium functions as low calcium, although the actual figures may be normal or even higher than normal, is found in the fact that some of these cases are complicated by tetany. Tetany does not occur with such frequency as in coeliac rickets, but nevertheless it is a well recognised complication of renal rickets.

Now the combination of tetany with rickets is always associated with a low serum calcium, and the onset of tetany is dependent not only on the total amount of calcium but also on the amount of calcium ions. The work of Loeb, Matthews and others [10] shows that the excitability of the neuro-muscular mechanism varies directly with the ratio $\frac{Na + K}{Ca + Mg}$ and that increased irritability can theoretically occur, either from a decrease in calcium, or an increase in sodium ions. In infantile tetany the increased irritability is due to a decrease in calcium ions for the magnesium, sodium, and potassium in the serum are essentially normal (Kramer, Howland, and Tisdall [11].)

The problem of the occurrence of tetany in renal rickets is, however, even more complicated because the following additional data have to be considered. The injection of phosphates into animals and children has been found to raise the blood phosphorus, lower the blood calcium, and in some cases produce tetany. Binger [12] found that the injection of normal or alkaline phosphates into dogs produced all these results, but acid phosphates on the other hand, whilst lowering blood calcium and raising blood phosphorus, did not produce tetany. Klercker and Odin [13] administered acid and normal phosphates to children, with resulting lowering of calcium increase of phosphorus, and an increase of electrical excitability. In those cases in which latent tetany was present the administration of these salts produced acute tetany. In chronic azotæmic nephritis there is a retention of phosphorus with the production of a high blood phosphorus, but the blood calcium is low. Thus in a recent investigation, Boyd, Courtney, and MacLachlan [14] have found consistently low calcium values in such cases, and De Wesselow [15] has shown that the higher the retention of phosphorus in nephritis, the lower is the calcium in the serum. Although this inverse relationship does not hold in renal rickets, yet it seems very clear that the mere presence of a high blood phosphorus means a low calcium, and the consequent production of tetany unless some mechanism is brought into play to prevent its occurrence.

Fig. 11.—Radiogram (B.T.) illustrating woolly type of renal rickets. Note the large extent of the metaphysis, the stippling, and the appearance of subperiosteal erosion; the general osteoporosis but without the atrophic character of the bone in Fig. 2.

Fig. 12.—Radiogram of the same bones taken *post-mortem* showing some bending of the lower epiphyses of the radius and ulna on the shafts of these bones, and the irregular manner in which calcification is proceeding.

In dealing with the problems presented by renal rickets it is therefore necessary to find answers to the following questions:—

(1) Why is the serum calcium so frequently normal in renal rickets, although the phosphorus is high; whereas in azotæmic nephritis without rickets, and in animals and children after the injection of phosphates, the serum calcium is low?

(2) If the rickets is a low-calcium rickets, why does not tetany occur with greater frequency?

(3) Why does tetany occur in this form of nephritis and not in other form of chronic nephritis ?

(4) What is the evidence that the bone deformities are of rachitic origin and why does cure sometimes occur ?

We have seen that, contrary to what usually obtains in azotæmic nephritis and after the injections of phosphates, in renal rickets with high phosphorus the serum calcium may be normal or even higher than normal. It seems conceivable that the serum calcium is maintained at this level to prevent the occurrence of tetany, which is such a very serious complication, and to which the young and growing child is much more prone than the adult. Now the rise in serum calcium produced by the injection of parathyroid hormone in tetany parathyropriva and in normal animals is due to washing out of calcium from the bones (Greenwald and Gross [16]). It is therefore not improbable that in renal rickets there is a washing out of calcium from the bones with resulting osteoporosis and rickets and the maintenance of the blood calcium at such a level that tetany shall not occur.

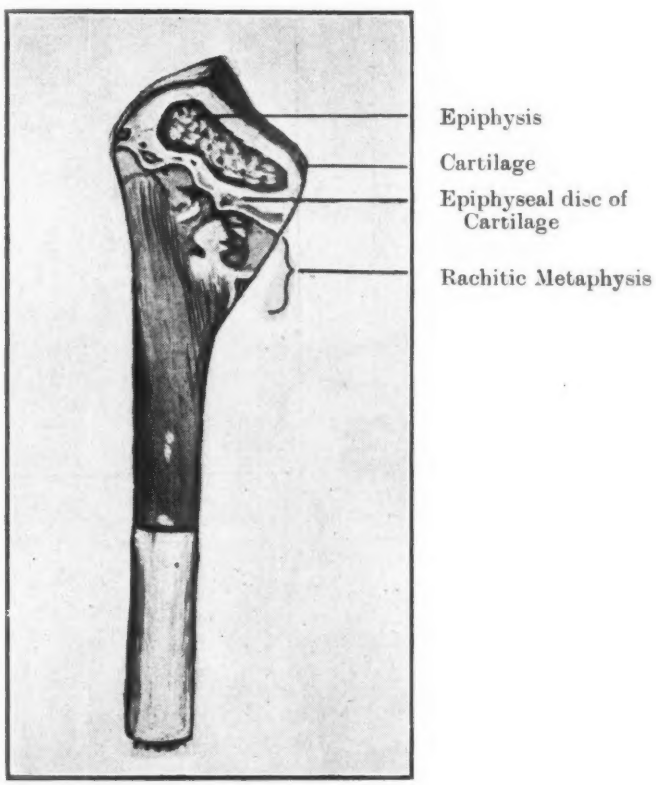


Fig. 13.—Drawing of the antero-posterior section of the lower end of the radius, seen in the two preceding radiograms (Figs. 11 & 12) showing the depth of the rachitic metaphysis, the presence of islets of cartilage deep in the metaphysis, and the bending of metaphysis and epiphysis on the shaft of the radius.

Recent work by Ross and Scriver [17] has demonstrated the possibility of such mobilisation of calcium from the bones. These workers have shown that in cases of infantile tetany, ammonium chloride, by virtue of its acid producing effect, causes a mobilisation of calcium from the tissues and presumably from the bones. According to Kramer [18] their results furnish an explanation of the fact that ammonium chloride, whilst capable of restoring calcium to its normal value in those cases of rickets in animals and children in which the calcium is low and phosphorus normal, is yet, contrary to expectation, not capable of producing healing of the rachitic process. The observations, indeed, show that such treatment would aggravate rather than ameliorate the condition.

De Wesselow and others have shown that in severe nephritis, there is usually a diminution in the bicarbonate content of the plasma and an acidosis and that these favour the ionisation of "the diminished amount of calcium present" [15], and so probably prevent the more frequent occurrence of tetany. The observations of Ross and Scriver show that the occurrence of an acidosis will also mobilise calcium ions from the calcium reservoirs, and estimations of the hydrogen-ion concentration show that a definite acidosis is present in renal rickets.

Considerable evidence has recently been forthcoming to show that the total content of calcium in the blood is not an index of the calcium ions in the circulatory fluids. There is no method by which the actual calcium-ion concentration of serum or plasma can be measured, but Pincus, Peterson and Kramer [20] have attempted to obtain some index of the ion concentration by using the method of ultrafiltration through collodion sacs under moderate pressure. Assuming that the calcium which does not filter is bound to protein and practically un-ionised, and that all the calcium that does filter is ionised, then the concentration of calcium in the filtrate is a measure of ionised calcium. They refer to the former as " bound " and the latter as " free " calcium.

An objection has been urged against the method of ultrafiltration under moderate pressure, that removal of the calcium ions by such means leads to the ionisation of the previously un-ionised calcium phosphate held in solution in the plasma, but this obviously does not invalidate the assumption of these workers that the calcium which does not filter is bound to protein. They found that in tetany there is a marked decrease in the " free " calcium in the serum, and that in chronic nephritis uncomplicated by uræmic convulsions the total calcium was decreased but the free calcium was normal, but that in one case with convulsions " free " calcium was reduced.

If the view of Pincus be correct, it is obvious that the reason tetany occurs in the nephritis of renal rickets and not in chronic nephritis is due to diminution, either relative or absolute, in the " free " as well as in the " bound " calcium. In this connection, however, it should be borne in mind that a degree of azotæmia comparable with that occurring in renal rickets, while not infrequent in adults, is of extreme rarity in childhood apart from renal rickets, and that the child is more liable to show tetany than the adult. I have not had the opportunity of estimating the calcium in the case of renal rickets with tetany and have

therefore not been able to test the correctness of this deduction, but in a case unaccompanied by tetany Lathrop (8) found that the "free" calcium was normal, although the total calcium in the serum was very low.

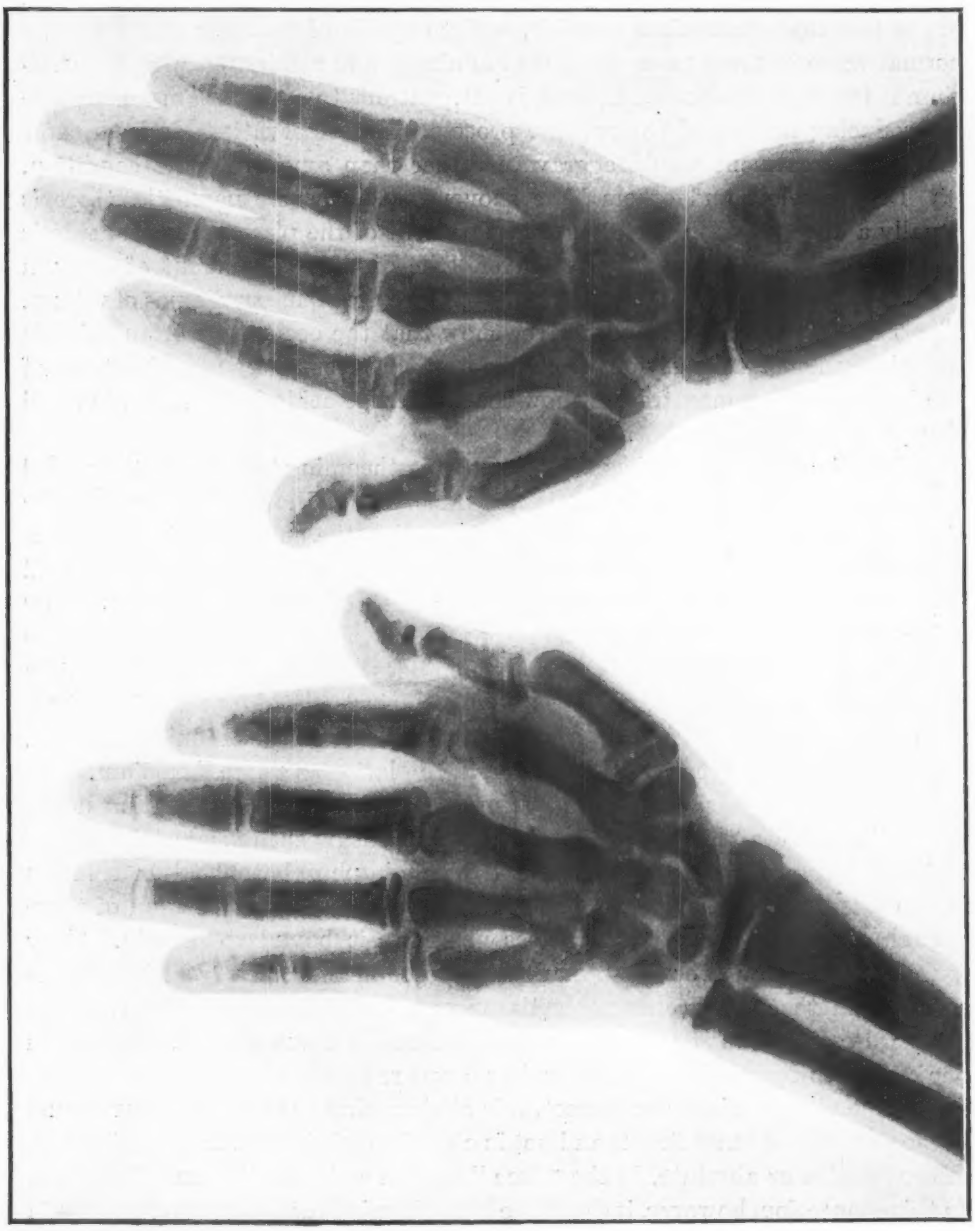


Fig. 14.—Radiogram of H.T. taken 30/10/25, showing the woolly type of renal rickets. Note the variations in the picture in the different bones. The metaphysis of the right ulna shows marked "honeycombing" and "stippling" whereas that of the left ulna shows erosion and woolliness.

What is the Evidence that the Bone Deformities are True Rickets?

The evidence, so far presented, that the condition is a truly rachitic one in the atrophic and florid types is based mainly on the results of X-ray examinations of the bones which show appearances at the epiphyseal line indistinguishable from those of rickets. The metaphysis is on the whole somewhat deeper than

Fig. 15.—Radiogram taken from the same case after nine months treatment with ultra violet light. The bone disease shows definite advance and the right radius shows more bending than in Fig. 14.

in ordinary low-phosphorus rickets, but the rachitic nature of the change would be admitted by anyone conversant with the X-ray findings in rickets. Histological evidence proving that the florid type of deformity is rachitic in nature has also been obtained in one of my cases (L.M.) This boy who showed marked infantilism, genu valgum, enlargement of the epiphyses at the wrists, a definite rosary, and rickets of the florid type in the radiogram, developed a fatal attack of uræmia shortly after admission to hospital. (Figs. 9 and 10). The autopsy was performed by Professor Haswell Wilson who reported on the histological examination of the bones as follows :—" Sections were prepared from a costochrondral junction, and from the lower epiphyses of the right radius. The changes seen in these two situations are essentially of the same nature. The line of ossification is broad and irregular and very little calcification is present in the matrix of the cartilage. The columns of cartilage cells are distorted and broken up by irregular masses of vascular osteoid tissue. Much fibrous tissue is seen between the trabeculæ of osteoid tissue and of the spongy bone beyond it, and in this a few detached islands of cartilage are lying. The histological picture is indistinguishable from that of ordinary rickets."

With regard to the woolly type, the histological evidence already detailed and the radiograms show that the similarity between this type and experimental low-calcium rickets cannot be doubted. The results of blood chemistry also show that in all types when bone deformities are present, the calcium can be regarded as functioning as a low blood calcium.

There are two chief theories on the mechanism of the deposition of calcium phosphate as bone ; that of Howland and that of Robison, the former being perhaps the more usually held. According to Howland, the rachitic bone tissue remains uncalcified just so long as calcium and phosphorus are supplied to it in such low concentrations that precipitation of tertiary (or normal) calcium phosphate cannot take place. The whole process can indeed be predicted with mathematical accuracy. Normally the serum and circulatory fluids are saturated solutions in which the calcium phosphate of bone is in equilibrium with the dissolved salt, and this in turn with calcium and phosphate ions, and this may be represented as follows :—

$$\underset{\text{Ionised.}}{\left[Ca^{++}\right]^3 + \left[PO_4^{\equiv}\right]^2} \rightleftharpoons \underset{\text{In solution unionised.}}{Ca_3(PO_4)_2} \rightleftharpoons \underset{\text{Solid in bone.}}{Ca_3(PO_4)_2}$$

An increase of $Ca++$ or $PO_4^{\equiv}$ causes the reaction to proceed to the right and results in deposit of bone, whereas a decrease in concentration would result in some of the solid calcium phosphate in bone going into solution, the reaction proceeding to the left. Now according to mass action law, at equilibrium the product of the concentration on one side divided by the product of concentration on the other side is constant at constant temperatures and therefore we have :—

$$\left[Ca^{++}\right]^3 \times \left[PO_4^{\equiv}\right]^2 = K\left[Ca_3(PO_4)_2\right].$$

Tertiary calcium phosphate is a sparingly soluble salt and in such $\left[Ca^{++}\right]^3 \times \left[PO_4^{\equiv}\right]^2 = K$. This K is called the solubility-product constant and whenever the product of the concentration of calcium and phosphate

ions becomes greater than the solubility product solid calcium phosphate will be deposited.

The occurrence of carbonic dioxide in considerable concentrations in the serum has, however, an influence on tertiary calcium phosphate which may be expressed thus :—

$$Ca_3(PO_4)_2 + 2H_2CO_3 \rightleftharpoons 2\ Ca\ HPO_4 + Ca(HCO_3)_2 \rightleftharpoons [Ca^{++}]^2 + [HPO_4^{=}]^2 + [Ca^{++}]^2 + [HCO_3^{-}]^2.$$

If the CO_2 tension of this solution is reduced, the reaction proceeds to the left and calcium phosphate is deposited. Howland suggests that because cartilage and the trabeculæ of bone are inactive tissues, it is to be expected that the CO_2 tension would be low in them, and it is in them that precipitation occurs if the solubility product be exceeded. The truth of the foregoing general principles can, he states, be proved by clinical observations, using as factors for a rough product the total concentrations of calcium and phosphorus in serum, each being expressed in milligrams per 100 c.c. This product in the normal child is between fifty and sixty. " When the product is below thirty rickets is invariably present. When it is above forty either demonstrable healing is taking place, or there has never been any rickets. With products between thirty and forty rickets is usually present [21]."

Robison on the other hand, does not agree that the deposition of calcium phosphate is purely a physico-chemical process, such as is outlined above. His hypothesis may briefly be summarised as follows (Kay [22]) : " the osteoblasts and the hypertrophic cartilage cells of the young animal secrete a very active phosphatase which, by hydrolysing the phosphoric esters of the blood, brings about a local increase of $PO_4^{=}$ concentration. The solubility product of tertiary calcium phosphate is thereby exceeded and the deposition of this salt occurs in the ossifying zone."

It is of interest to note that Howland [23] in his last paper on this subject, written in collaboration with Shipley and Kramer, published shortly before his death, appeared to regard the physico-chemical theory as not the complete explanation since he concludes : " the process is clearly not one of simple precipitation, it depends upon the activity of living tissue. It cannot occur unless the concentration of calcium and phosphorus in the serum and presumably in the fluid bathing the cells, exceeds a certain minimum value."

Now it is clear that in all my cases on most occasions the product Ca × P is greatly in excess of fifty, and for this reason Lathrop will not accept the view that the bone deformities of renal infantilism are true rickets. The co-existence of bone changes—which in my view are undoubtedly rickets—with a Ca × P product of over fifty may be difficult to explain, but the occurrence cannot be denied, and therefore some explanation must be sought.

A series of papers by Holt, La Mer and Chown [24] furnishes some interesting points in this connection. They have found that the blood serum is normally supersaturated with tertiary calcium phosphate and have devised a method by which the calcium and phosphate ions can be calculated. They have also

calculated out the product of the ions $[Ca^{++}]\times[PO_4]^2$ in rachitic and normal sera in order to ascertain the relationship between the ion product and the solubility product constant for $Ca_3(PO_4)_2$ in blood serum. The results obtained show that even in active rickets the ion product is considerably greater than that

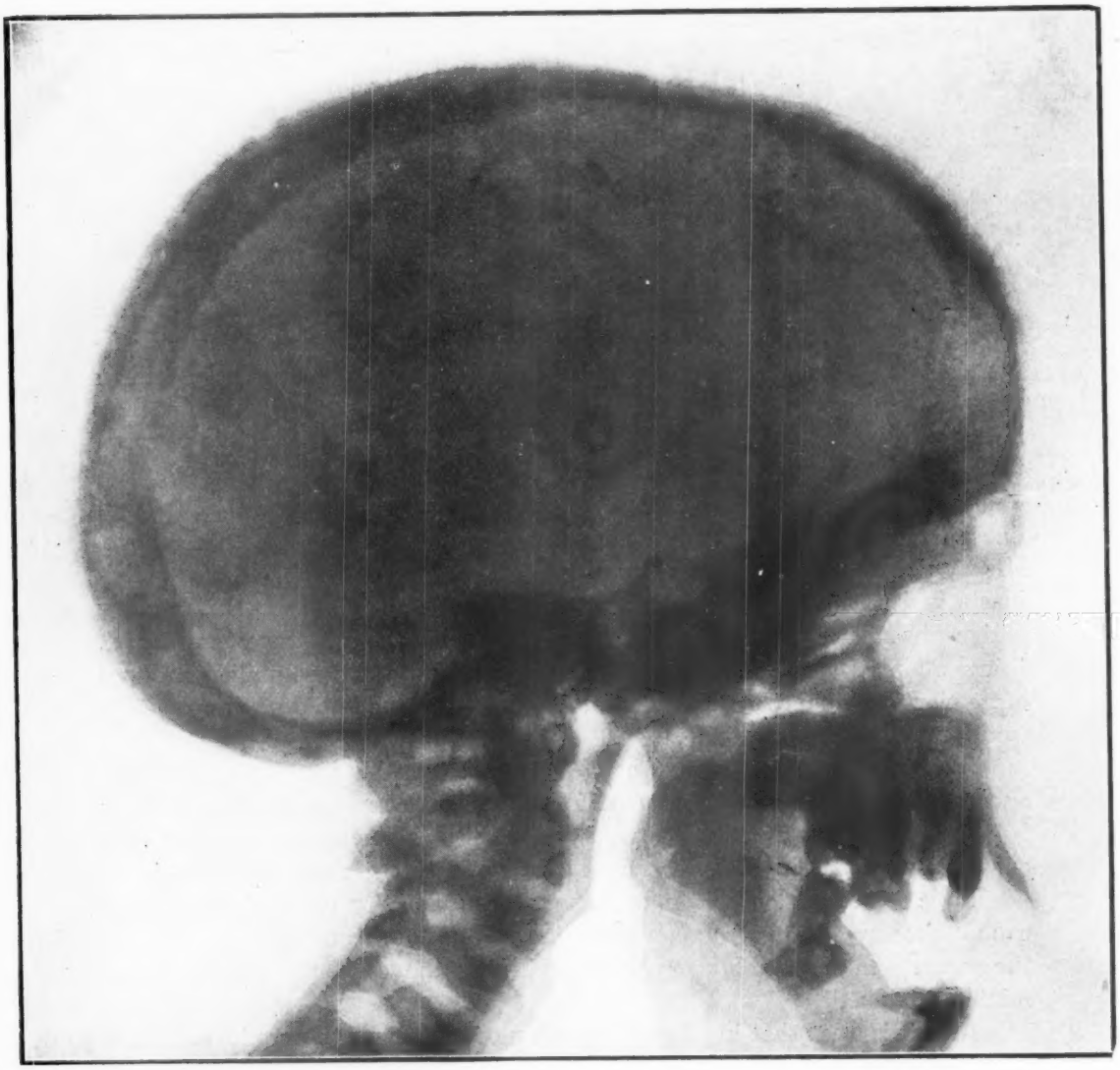


Fig. 16.—Radiogram of skull from the same case as Fig. 14, and 15. The bones of the vault are greatly thickened and show "stippling" to an extreme degree.

required to precipitate tertiary calcium phosphate. Precipitation of tertiary calcium phosphate is comparatively a slow process, and proceeds with very great slowness when the ion product is only slightly in excess of the value of the solubility product constant, and therefore they think that in active rickets calcification is proceeding but so slowly that it is not ordinarily detected. In

support of the latter view there is given a personal communication from Shipley to the effect that rats fed on a diet rich in phosphorus but poor in calcium (McCollum's diet 3143), showed during the first six weeks a broad rachitic metaphysis free of calcium, but as the condition became chronic the metaphysis not infrequently became peppered throughout with fine deposits of lime salts. This description appears to correspond very closely with the " stippling " which occurs in some cases of the woolly type of renal rickets. These workers would define rickets " not as a state in which the concentrations of calcium and phosphate are so low that $Ca_3(PO_4)_2$ cannot be precipitated, but as a state in which, as the result of lowered ion concentration, $Ca_3(PO_4)_2$ is deposited so slowly that new bone production exceeds it in rapidity, and consequently uncalcified bone or osteoid tissue is produced." Such a conception explains the fact that in adult life after growth has finished, the concentrations of calcium and phosphorus are similar to those found in active rickets in infants.

With regard to the Ca × P product, they say that whilst a high product is usually associated with a high ion product and *vice versa*, yet it is only a rough guide to the true ion concentration and not as good as the ion product for several reasons, the chief of which is that it does not give enough weight to calcium concentrations. The suggestion is made that the ion product should be used instead of the Ca × P product, and that it should be expressed as the negative logarithm of molecular concentration (p product) as is so usually done with hydrogen ions (pH). If this be done, the p product for active rickets is usually greater than 24·10, whereas when the disease is healing or absent, it is usually less than 24·10. The p product for the solubility-constant of tertiary calcium phosphate in blood serum is 26·0.

For the purpose of comparison with these results the p product has been calculated in all my cases, and in every instance the result is less than 24·10, *i.e.*, rickets should either be healed or absent. The calculations have been made on the assumption that the pH of the blood serum in each case was 7·35, but we know that in chronic nephritis an acidosis occurs, and Holt has shown that small variations in pH produce considerable changes in that fraction of the total phosphorus ionised as $PO_4^{\equiv}$. The pH of the blood has been estimated in only one of my cases. The method used was that described by Drucker and Cullen [19] and gave a pH of 7·16. When the correction was made for this factor a higher p product was obtained but it did not exceed 24·10, being in fact 23·40. The influence of acidosis is, however, well demonstrated if the p product of the case described by Lathrop [8] to which reference has already been made, be calculated. The Ca × P product in this case was 43·7, a result which made him regard the bone changes as non-rachitic. The pH of the blood was 6·98 and the p product at that pH is 24·30, a figure which is quite compatible with active rickets.

The importance of acidosis has also been emphasised by Freudenberg and György [25] who have expressed the relationship between the calcium bicarbonate and phosphate ions, and the hydrogen ion concentration of the blood by the following formula :—

$$\frac{[Ca^{++}]\ [HCO_3^-]\ [H\,PO_4^{\equiv}]}{[H^-]} = K$$

or, in words, the concentration of calcium ions decreases as the bicarbonate and phosphate ions increase, and increases as the hydrogen ion concentration increases, *i.e.*, as there is a shift of the reaction to the acid side, and *vice versa*. Now, as we have seen, in renal infantilism there is an increase in phosphate ion, sometimes a diminution in carbon dioxide, usually an acidosis and not infrequently a normal calcium. This must mean, if the formula be correct, that the increase in phosphate ion is balanced by the degree of acidosis.

Finally, I would again draw attention to the similarity between the effects produced by the injection of parathyroid hormone and the findings in renal rickets. In the former the calcium and phosphorus in the blood are both raised above normal, *i.e.*, the blood previously supersaturated becomes even more supersaturated, so that it is clearly possible under such conditions to obtain a Ca × P product that exceeds fifty and to obtain this increased calcium from the body reservoirs (of Greenwald and Gross[16]).

Admitting, therefore, that it is possible under certain conditions, e.g., acidosis, after administration of parathyroid hormone, for the factor Ca × P to exceed fifty, the occurrence of rickets in renal infantilism becomes easy of explanation, because the calcium relative to the phosphorus is low and we thus have one of the conditions laid down by Howland under which rickets will occur. Further evidence in favour of this view is found in a case of florid rickets (N.H.) in which cure occurred. (Figs. 4, 5, 6, 7, 8.) When admitted into hospital in January, 1926, this child was severely ill with symptoms of uræmia. Her condition improved and in August the rickets had completely healed. As the bone healed the blood phosphorus fell, whereas the calcium remained at about the same figure until when the cure was complete the phosphorus was only slightly above the normal figure. I do not think that any explanation other than alteration in the relative proportions of concentration of the calcium and phosphorus can explain such a cure.

I would, therefore, submit that the clinical, radiographic, histological, and chemical evidence presented, show that the bone deformities are rachitic in nature.

Earlier in this paper I have made the statement that I have not been able to produce a cure in renal rickets by ultra-violet irradiation, whereas in coeliac rickets such treatment results in cure. The explanation of these results is probably to be found in the fact that ultra-violet light raises the blood phosphorus by increasing phosphorus absorption, and therefore treatment by this method makes the disparity between the calcium and phosphorus even more marked. Indeed, I think the tendency is very definitely to make the disease worse. If the radiograms of the case H.T. be examined it is obvious that the disease is more marked after nine months irradiation (Fig. 15) than before this treatment was started (Fig. 14). During that period the bending of the lower limbs also increased greatly. It may be objected that this is only evidence that the disease has progressed in spite of, and not because of, the treatment.

If the treatment were not to blame it is difficult to explain the rapid drop in blood phosphorus from 8·5 mg. to 4·7 mg. per cent. which occurred in twenty days after this treatment was stopped, and which was unaccompanied by any fall in blood urea or non-protein nitrogen. During the same period the blood calcium also fell, but not to a degree at all comparable with the fall in phosphorus, and this also may quite probably have been due to the cessation of ultra-violet ray treatment.

Complete cure does, however, occur, as we have seen, both in the florid and atrophic types, and even in the woolly type there is evidence of attempts at cure. The mechanism differs somewhat according to the age of the child. Those rare cases of renal rickets which survive to sixteen years and over, have reached for them almost the limit of the growth period, and therefore the call to mobilise calcium to prevent tetany becomes less insistent and there is also less required to ossify cartilage. This is particularly the case when the epiphyses have united with the shafts of the bones, and the growth period has ended. In children suffering from renal rickets the blood urea is always high, but it varies considerably, and at times for some unexplained reason the blood urea rises even higher. At the same time the child shows signs of uræmia, *e.g.*, vomiting, headache, drowsiness, etc., or the blood urea remains at a higher level for some time without such marked signs of uræmia, but with some considerable increase of the general symptoms. After a time a degree of recovery usually occurs, the blood urea falls and the child returns to its normal condition. In precisely the same way and correlated with the rise in blood urea, the blood phosphorus rises. As the child recovers the phosphorus is better excreted and the blood phosphorus, as in the case already quoted, may reach a normal figure and the calcium phosphorus ratio thus become normal. Also owing to the fact that the phosphorus is nearer the normal level, the blood calcium would tend to become normal, and therefore there would not be any need to mobilise calcium from the bones to prevent tetany. In either case healing of rickets will occur. Such an explanation accounts for cure, for relapse, and also for the state of " flux between healing and repair " referred to by Shipley.

The factors necessary for the prevention of rickets are usually stated to be an adequate supply of calcium, phosphorus, and Vitamin D in the dietary. Renal rickets develops and persists in spite of an adequate supply of all these factors, and hence the suggestion of Shipley that under certain conditions rickets may have an endogenous origin appears to be incontrovertible. In view of a statement made by Ashcroft that " sufficient evidence has been found to warrant the suggestion that the disease may be due to a fibrosis of the suprarenal gland "[26] I would add that in the case of L.M. the suprarenals were large and showed a normal appearance under the microscope. The suggestion of Ashcroft appears to be based on very slender evidence, especially as Swingle[27] has recently shown that whilst total removal of the adrenals of cats results in a rapid rise of blood phosphorus, blood urea and non-protein nitrogen, these changes do not occur as long as any adrenal cortex remains.

The answers put forward to the questions asked may therefore be summarised thus :—

The bone deformities associated with renal infantilism are those of true low-calcium rickets, and have their origin in the inability of the kidney properly to excrete phosphate. As a result of this inability on the part of the kidney to excrete phosphorus the blood calcium becomes relatively low and rickets occurs. During those periods in which the kidney is functioning better and excreting more phosphorus the calcium-phosphorus ratio becomes relatively more normal and healing may take place.

The blood calcium is maintained at a higher figure than is usual in severe nephritis with phosphate retention, by the mobilisation of calcium from the bones, and this is another factor in producing rickets. When the phosphate is better excreted the serum calcium automatically tends to rise to a higher level (see Freudenberg's and György's formula) and therefore the necessity for obtaining calcium from the bones is lessened and healing may occur.

The mobilisation of calcium from the bones may be considered as a protective mechanism for the prevention of tetany and therefore be, in part, the explanation of its infrequent occurrence.

Another factor in the prevention of tetany is the occurrence of acidosis, for this also mobilises calcium from the bones and favours its ionisation.

Tetany sometimes occurs in renal rickets because the " free " calcium is reduced relatively and may indeed be reduced absolutely; whereas in chronic nephritis the free calcium is normal, the reduction in calcium being due to diminution in the amount of " bound " calcium.

Conclusions.

1. The bone deformities of renal infantilism are those of true low-calcium rickets. The radiograms show that a case of renal infantilism may develop bone changes of one of three types :—

   (*a*) atrophic rickets.
   (*b*) florid rickets.
   (*c*) woolly rickets.

2. The primary cause of renal rickets is the inability of the kidney properly to excrete phosphate, *i.e.*, a true endogenous rickets exists.

3. The blood shows marked lipæmia, nitrogenous and phosphate retention, and an acidosis.

4. Blood calcium, whilst low compared with blood phosphorus, frequently shows normal values, in contra-distinction to what usually obtains in azotæmic nephritis and after the injection of phosphate. The suggestion is made that this is due to mobilisation of calcium from the bones as a preventative mechanism against tetany.

5. Healing of rickets may occur in those periods in which phosphorus excretion improves materially, or when the growth period is over.

6. Treatment of renal rickets by ultra-violet irradiation is contraindicated, and evidence is produced to show that such treatment aggravates the bone changes.

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THE INFANTILE FACTOR IN FAILURE OF BREAST FEEDING.

BY

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The observations to be detailed were made at the Salomon's Welfare Centre over a period of approximately two years. All cases of failure to breast-feed were kept under observation as much as possible during this time with a view to finding out why they failed. Excluding the cases where some force outside our control deprived the child of his milk, or where the mother took matters into her own hands and lost the milk through her own mismanagement, we gave a series of test-feeds as often as practicable, during which the behaviour, method of sucking and other points about the child, and also the mother's mode of handling it, were noted. X-ray examinations of the stomach were also made in many instances. The various cases soon fell into groups, so that it became possible to see what are the really common and important causes of failure to breast-feed. To know where the dangers lie is to be prepared to try to avoid or overcome them. Breast-feeding in every case is the ideal one would like to aim at. The number of breast-fed babies at this Centre is, as a matter of fact, high, but it might be higher still. It was as a step towards the goal of universal breast-feeding (which can never of course be perfectly achieved) that this research was begun.

A word as to the opportunities of observation at the Centre. The area served by the Centre is a very small one, and this has its advantages. For the lives, the homes, the histories and many other facts about the parents are very well known to the Staff of the Centre. A great deal of intimate information was available, which could not have be enobtained so well with a larger area. The proximity of the great hospital was another help to us. The two centuries since Guy's Hospital was founded have not left the folk who live around it unimpressed : generally speaking they have faith in it. So we find among them a confidence in carrying out treatment, a readiness to act on advice, and a regularity of attendance, which is greater, I am sure, than it would be without the long tradition of the Hospital. There has been one disadvantage, and that is lack of space at the Centre. A special room where all the test-feeding could be carried out, under supervision, would have been a help. Then the mothers could leave their babies for the day and come up at intervals for test-feeds, perhaps repeating it for several days. Very complete and concise information should be obtainable in this way. The advantage of such a scheme in the case of the harassed mothers and the unrestful child goes without saying. But as it was, the opportunities for prolonged observation were not so great as we should like.

Scope of Observation. This series comprises every case in which breast-feeding failed wholly or in part, from whatever cause. Total failures were all

included : so also were those in which the breast-milk had to be permanently supplemented with some other food, as they were regarded as partial failures. Cases in which complete breast-feeding was re-established were not included : they form a class by themselves. The age limit was up to six months. Some arbitrary limit was necessary. This was chosen since it is the age at which Nature seems to hint, by providing the child with teeth, that pure breast-feeding may be supplemented with something else. Further, according to Starling, the quantity of breast-milk diminishes in any case after this time. A period of two years was occupied with the observations and during this time 115 cases were recorded.

At the outset they fall into two groups, those controlled and those uncontrolled. In the former some abnormality of child or mother was at least partly responsible for failure. In the latter, either mismanagement on the mother's part, or some accident or interference from outside was the cause of failure. In them there was no intrinsic reason why the breast-milk should ever have been lost, and no abnormalities to account for it. The uncontrolled make up a large number, nearly half. They are not to be considered genuine cases of breast-failure ; that is, had there been no other food but breast-milk available, the child would have continued to be breast-fed in all of them. But they are of considerable interest since they show what a large number of cases of failure to breast-feed are avoidable ; or in other words, how many mothers fail to carry out a simple function through their own fault. For it may at once be said that those who failed only through force of circumstances were very few indeed. Further, we see what are the mistakes they make, and how they lead to failure.

I. Failure of Breast-Feeding in Group of Uncontrolled Cases.

The uncontrolled cases are best taken first. They are divisible into cases of Mismanagement of Feeding and cases in which some External Cause was the factor.

A. *Mismanagement of Feeding.*

(27 cases, or 23·5% of the total.) In this group there was failure, complete or partial, to breast-feed owing to mismanagement on the mother's part, and not to any disease in the child or mother. In 24 out of the 27 instances incorrect supplementary feeding was responsible.

In order to explain the mistakes, it is necessary to give a brief account of what we consider the best way of supplementing an insufficient supply of breast-milk. If a shortage of breast-milk is suspected, a series of test-feeds is done to determine how much milk the child sucks. The amount that can be obtained by manual expression after the feeds is also taken. The average of the amount sucked in a number of feeds may show a defect from the amount calculated as necessary for the child's weight and age. If this is so, then the expressed milk is also ordered to be given by spoon after the child has sucked. If there is still a shortage, the amount is made up by giving a feed of cow's milk and water slightly sweetened after the expressed milk, also with a spoon. Suppose, for instance, the calculated amount required for a child was 5 ozs. per feed, and

that the average sucked was only 3½ ozs., with an average of ½ oz. expressible in addition ; the child would be put to the breast first, then given the expressed milk, and finally 1 oz. of a mixture of cow's milk and water with a little sugar or extract of malt, making the total up to 5 ozs. In practice, it is a good plan to give a little under the requirements : it is certainly important never to give more. Too big a meal at one feed means diminished appetite for the next and diminished suction of the breast. The amount of milk will then not only tend to go up, but may even get smaller. The advantage of the method is that the breast is thoroughly emptied each time, and thereby receives the proper stimulus for a fresh secretion for the next meal. The amount sucked then tends steadily to go up ; it is checked by further test-feeds, and as it rises, the supplementary cow's milk is diminished and finally abolished altogether.

Interpolation of Bottle-Feeding. (8 cases.) This is the commonest and most disastrous mistake in supplementary feeding. It is absolutely essential in all cases that the supplement should be given by spoon. Children frequently prefer feeding from a bottle to feeding from the breast. Even when breast-feeding is proceeding normally this is often so, and to introduce a bottle is to see the amount of breast-milk secreted gradually dwindle. For where there is any difficulty in feeding, the child will inevitably forsake the breast for the easily running bottle. Gradually less and less breast-milk is taken, and the bottle-feeds grow larger and more numerous until breast-feeding goes altogether, if the bottle is not abolished in time. With spoon-feeding the case is different : there is no incentive to the child to abandon the normal suction for such a tedious way of being fed.

Incorrect Food as Supplement. (7 cases.) Cow's milk diluted and slightly sweetened is the supplement that rarely fails to give satisfactory results. Or if, as very occasionally happens, the home conditions are so bad that fresh cow's milk is not considered safe, a dried milk is used. The mistakes made were all identical, namely, the giving of a sweetened condensed milk as a supplement. This substance is not only an ill-balanced food in itself, but it has a disturbing effect on breast-feeding. It is a fact that it is given successfully sometimes, and even given under medical advice ; but it is far too risky to be advisable. The risk lies in the peculiar deliciousness of its sweet taste to the infant, who, having once experienced it, may thenceforth take no further interest in his natural food. To introduce a sweetened condensed milk often signalises the end of breast-feeding ; and if the condensed milk is given out of a bottle, the end is so much the nearer.

Unnecessary or Excessive Supplement. (6 cases.) A mistake often made si giving supplementary feeds without first ascertaining by test-feeds how much, if any, is needed. As a rule the breast-feeding can be rescued by promptly cutting down or removing the supplement. But in these 6 cases, the mothers persisted in their mistake in spite of advice. In 3 no supplement

at all was needed but one continued to be given. In 3, that given was larger than was needed. The overfed child now fails to suck properly at the breast. The normal stimulus to secretion of breast-milk fails, and the amount secreted diminishes. Often there is excess of breast-milk to start with, as in three of our cases, but the trifling dyspepsia that results from this is mistaken for hunger : the unnecessary extra feeding is persisted in, and the infant's appetite rapidly declines. The heavy flabby breasts that often go with an excess of milk are very sensitive to the withdrawal of the suction-stimulus. They soon begin to dry up, and so the paradoxical position is arrived at, that an excess of breast-milk has led to its disappearance.

It ought to be a golden rule in breast-feeding that a supplement should never be ordered without a preliminary series of test-feeds. And, further, that the combined feed should never be above the child's needs, but if anything a trifle below.

Interference with Physiological Inanition. (5 cases.) For a little while after birth, the amount of milk taken is insufficient for the needs of the child. Weight is often lost for the first few days. The free secretion of milk is later produced by the child's suction. If the child does not suck very vigorously, the period of inanition may be prolonged. Strictly regular feeds, and perseverance in putting the child to the breast, are called for when this happens. Many mothers, however, quite fail to understand this, and put the child on extra feeds of some other food ; the suction then grows feebler, and the milk supply dwindles still further or disappears. The dangerous time seems to be about the end of the first fortnight, when the mother is beginning to get up and about. There are other distractions now and a great temptation not to persevere with the breast-feeding. In our cases, the earliest failure was at 10 days, and in the latest, partial breast-feeding was maintained for ten weeks.

These four mistakes just described emphasise one fact, that is, the danger of interference with pure breast-feeding except under guidance of skilled advice and careful control. From the pitfalls into which the uncontrolled cases have fallen we can summarise what mothers should particularly avoid doing.

(i) They should not introduce any supplementary feeding unless there is a proved shortage of breast-milk.
(ii) They should not give an amount that is greater than is necessary to bring each feed up to the quantity required for the infant's age and weight.
(iii) They should never give a supplement by bottle.
(iv) They should not give a food that is likely to spoil the child's appetite for breast-milk.
(v) They should not interfere with the preliminary period of physiological inanition.

Too Frequent Feeding. (3 cases.) These are totally different from those described above. The child was kept to the breast, but the breast was exhausted by being too frequently used. They are illustrations of the old country saying that the cow that is always milked is the one that loses her milk. Four-hourly feeding is the method that we find generally gives the best results. Too frequent feeding causes loss of appetite and dyspepsia ; the good hearty suction of the infant at right intervals, draining the breast dry at each meal, is wanting. Instead, there is a poor irregular suction, accumulation of residual milk, and ultimately a danger of failure of the secretion altogether.

Age Incidence. These cases of mismanagement generally occur fairly early. The earliest age at which weaning took place was 10 days. The latest was 16 weeks. The average was 8 weeks.

B.—*External Causes.*

(30 cases.) A large group in which some external influence determined the complete or partial weaning of the child. There is only a solitary case among them in which the weaning took place of necessity, and that is one where the mother died. In all the others, feeding could have gone on. Some of the reasons for giving up breast-feeding were excusable, as, for instance, where the mothers were obliged to work ; others were quite futile and even disgraceful. They may be briefly described.

Folklore. (3 cases). Fear of the effect of menstruation on the milk made three mothers wean their children. The effects are in truth either none at all or only sufficient to cause a slight temporary halt in the upward climb of the weight.

Work. (4 cases.) The necessity of earning a living in shops or factories made the mother wean her child in these cases.

Pleasure. (2 cases.) These two gave up feeding their children in order to have more time for enjoyment. In both cases weaning took place during a seaside holiday.

Separation. (2 cases.) Here the mother went into Hospital without the child or vice versa. In the mother's case it was scarlet fever, a disease in which it is generally considered possible to nurse the child. In the case of the child, it was the rare condition of congenital duodenal atresia with the still rarer result of recovery after operation. The mother had to make daily journeys to feed the child, but even so did not succeed in getting the milk supply well established. This case is difficult to place, since it might be argued that the severe illness and operation prevented the child from sucking properly. I have no observations on this point, however, and have left it rather conjecturally as a case in which separation from the mother at such a very early age was the determining factor.

Death of mother. (1 case.)

Advice of relatives, friends, etc. (6 cases.) The offenders were grandmothers, " gamps " and other banes of infant welfare.

Advice of Medical Practitioners. (10 cases.) Looked at solely from the mother's interest, there was reason for weaning in some. One at least was wasting rapidly from active phthisis. Excluding this one there seemed to me no serious disease in the other 9. The justification for depriving the infant of its natural food in these depends entirely on the point of view. At any rate, secretion would have gone on normally.

Suggestion. (2 cases.) There seemed no adequate reason why the mother should lose her milk here except that she had done so with a previous child and was convinced that she would do so with the present one.

Age Incidence. The ages at which weaning took place were of course, very various, ranging from 1 to 23 weeks. The average was 11 weeks.

II. Failure of Breast-Feeding in Group of Controlled Cases.

In these, if there was any mismanagement, it was not at any rate uncontrolled by us. All the uncontrolled mistakes described under the first heading were either avoided altogether, or only occupied a secondary place. All cases in which some external influences beyond our control were the cause of the failure, were likewise ruled out. We are therefore left with cases in which the kernel of the matter was an actual failure of the secretion of the breast, dependent mainly on some abnormality in child or mother, or both. This is not to say that the failure was inevitable always. On the contrary, in many cases, the abnormality might have been overcome, but was not.

The cases are divided into groups, namely, those due to disease of the mother, two, and those due to disease of the child, in which was included the condition of nervous unrest.

A. *Due to Disease in the Mother.*

(20 cases, or 19·1%). This group is clearly divisible into disease of the breast and nipple and disease of other organs.

Diseases of the Breast and Nipple. (6 cases.) Cracked nipples were responsible for two failures here, the pain of the child's suction being in each case the cause, and not any diminution in the amount of milk, at any rate at first. Indeed, test-feeding showed, in both cases, a fair quantity. But after a month or so of suffering while, in spite of treatment, the nipples were refusing to heal, the mothers refused to submit any more to the pain of it and put the child on a bottle. There was, therefore, no failure of lactation here, but a failure (very comprehensible) to bear pain.

Retracted Nipples. (1 case.) Drawing the nipples out with a breast-pump, the milk drawn off being given to the child, generally resulted in their elongation. Once the child can get hold of them, the rest is done by his suction, so this is not a frequent source of failure.

Deformity of Nipples produced by scarring, however, does not yield to this treatment, and was responsible for another failure.

Abscess of Breast (2 cases) should stimulate rather than discourage efforts at feeding. If the abscess has been opened, however, feeding from that breast may be impossible for surgical reasons. The child may still be tided over temporary difficulties by supplementing properly, and ultimately be brought up on one breast only. This is what happened in one of our two cases. For six weeks after the opening of the abscess, the child's weight ascended regularly and well on the single breast ; but as there had been some mastitis in this side, the mother became convinced that the milk would be harmful to the child and (probably on the advice of friends) put him on a bottle. In the other case, a supplement was needed, which was gradually reduced from 3 oz. to $1\frac{1}{4}$ oz. as the amount of milk increased ; but again, the mother fell into the hands of the enemy and foolishly introduced a bottle, with the usual result.

It is clear that in only two cases out of six was there a real failure of the mother to supply the child with milk, namely in the case of retracted and the case of deformed nipples. In the remaining four, there was a partial failure owing to abscess, which, however, was on the road to becoming a success. A suggestion of failure and a precipitate rush to bottle-feeding was the real cause in this and the other abscess case ; inability to bear pain in the remaining two. So a true failure of lactation occurs in two instances only.

General Maternal Disease. (12 cases.) Two cases were of mitral stenosis, in one of which the mother's mismanagement had as much to do with failure as ill-health. At any rate we know that she surreptitiously gave the child beer. In the other case weaning was carried out by the doctor's orders, and there was no failure of secretion.

A severe dental abscess caused a sudden failure of breast-feeding in one case. This mother was a bad manager, however, who was always desirous of introducing artificial feeding, and she made no attempt to re-establish. Of more general causes we find a feeble mother unable to bring up twins without supplementing ; a primipara of 36 also having to supplement, and a worn out mother of ten children doing the same. I include also three cases under this heading in which an actual shortage of food was pretty certainly the cause of complete or partial failure. There were two more in which the mother ascribed it to shock or worry. How much was due to a real failure of breast-milk, and how much to lack of attention to feeding at a time of distraction I cannot say, but I suspect the latter as the more important cause.

There remains one case of a mother who worked at an unhealthy occupation. Soon after she returned to work, the child's weight steadily refused to rise until it was taken off the breast. Test-feeds showed an ample quantity of milk ; so it was quality and not quantity that was lacking. (This mother has now given up work and is breast feeding a second child with perfect success.)

Of these 12 cases, there was a failure, complete or partial, to breast-feed in seven which can be attributed to a genuine inadequacy of milk, three being due to poor health of mother, three to insufficient food and one to unhealthy occupation. In five it can be attributed to lack of proper attention or management as well.

Thus out of these 20 cases of failure owing to Disease of Mother, there are only 9 which could not have been avoided, being genuine cases of failure of lactation. They comprise :

Deformed or Retracted Nipples	2
Poor Health of Mother.....	3
Insufficient Food	3
Unhealthy Occupation.....	1

Pain, ignorance, superstition, lack of attention and mismanagement made up the rest.

Age Incidence. The average age at which weaning took place in these nine cases was 8½ weeks, those in which disease of the breast was the cause occurring very early ; those in which poor general health, poverty and other such adverse conditions were the cause, dragging on to from 14—20 weeks. There are thus two different age averages. Where there is deformity or disease of breast or nipple, there is failure of suction and disappearance of milk which occurs early. Where there are general adverse conditions working against a free secretion of milk, but no interference with the suction-stimulus, disappearance is quite late.

B.—*Disease of Child.*

(38 cases or 33·1%). These are divisible into (i) Local causes in the mouth ; (ii) Feeble power of suction; (iii) Respiratory and (iv) Alimentary Diseases, (v) Nervous unrest.

(i) *Local Causes in Mouth.* (4 cases.) All were the same, namely, hair-lip and cleft-palate. A child with such a deformity is quite unable to suck and although the breast-milk can be drawn off and given by spoon for a while, yet in the absence of the proper stimulus it is bound to fail in time. Where there is cleft-palate only, the outlook is better, since the fitting of an objurator may enable the child to suck, and we once succeeded in effecting complete re-establishment by this means. " Thrush " and other local conditions were not serious enough to cause any failures.

(ii) *Feeble Power of Suction.* (8 cases.) Prematurity caused total loss of breast-milk in one case and partial in another, through the failure of the infant to draw the breast well enough. Three wretchedly puny children of syphilitic mothers failed in the same way. Mongolism accompanied by emaciation and atelectasis caused a partial failure, also only attributable to feeble suction : there was abundant milk at first.

(iii) *Respiratory Disease.* (5 cases.) Much the most frequent is the nasal catarrh that is so common in infants, which, if allowed to run on unchecked, leads to a nasal obstruction. A child who cannot breathe through his nose is in a very difficult position when he comes to take the breast. The normal method of feeding consists of a series of sucking actions with the lips closed tightly round the nipple, respiration being carried on quietly and evenly through the nose. If the nose is blocked, the child has to pause every few seconds to take a breath through his mouth, often not wholly letting go of the nipple while he does so. The result is aerophagy. A great deal of air finds its way

through the open mouth into the stomach as well as milk. The effects of this may be seen by X-raying the child's stomach a few minutes after the meal.

Fig. 1.—Radiogram of stomach of infant with nasal obstruction taken five minutes after a feed stomach is distended with swallowed air.

The appearance of the stomach 5 minutes after a feed in a case of nasal obstruction is shown. The organ is distended with air, which is even passing on into the duodenum. Eructation of the swallowed air further interferes with suction ; appetite is lessened ; with lessened stimulus there is lessened supply and the amount taken tends gradually to decrease. If the child is resentful of these difficulties, and struggles or screams at the breast, the feeding becomes more and more difficult and finally there may be definite refusal to take the breast at all.

Other dyspnœas such as bronchitis or pneumonia, may cause interference with suction. But it is a fact, I think, that the breast-milk is seldom lost through them, so long as the child is not separated from its mother. None came under our observation.

(iv) *Alimentary Disease.* We found none that caused a failure of breast-feeding, except the rare case of Duodenal Atresia where the child was separated from its mother by being taken into Hospital. This is included under External Causes.

Age Incidence. The average age at which weaning took place was only 4 weeks. Those in which the cause was local in the mouth occurred at birth. Of the others, all but one occurred within six weeks.

In all these 17 cases the failure of breast-milk was believed to be genuine, and to be caused by interference with the normal stimulus of the child's suction. Whether it was due to deformity, to dyspnœa, or to mere feebleness, the result was the same ; and the disappearance was always early. This corresponds to what we already saw in the case of deformities or diseases of breast and nipple, in which the stimulus of suction also fails, and the milk " goes " early. To look at the matter in another way ; where the milk " goes " in the first few weeks, it is lack of suction that is responsible. And this may be produced by deformity or disease in the apparatus of suction by dyspnœa, or by an enfeebled condition in the child. But it is *not* due to any ill-health in the mother. This, if it occurs at all, occurs later.

(v) *Nervous Unrest.* (21 cases.) By this condition we understand the numerous cases in which the child is in a state of anxiety and unrest. In all our cases it was observed that the mother as well as the child was disturbed. In no case was there any difficulty when the mother remained entirely placid. The child of a stolidly unemotional mother may cry it is true, from whatever cause ; but his method of feeding is not interfered with. But with a nervous mother the matter is entirely different. Directly there is the slightest upset she begins to worry, and the child is quick to appreciate her anxiety. Instead of a soothing influence he feels a disturbing one ; instead of a quiet confidence, there is irritability or timidity. He quickly shows his resentment of his uncongenial environment, generally by passionate fits of screaming. Dyspepsia and difficulty in feeding soon follow. Very often the mother with a desperate desire to improve things makes grave mistakes in management, such as the introduction of artificial feeding by a bottle, or a recourse to too frequent breast-feeding in an effort to hush the child. The result of either is likely to increase the dyspepsia. And as the child's symptoms grow worse, the maternal anxiety increases too, to which again the child reacts still further by screaming, dyspepsia, sleeplessness and failure to gain weight. Finally both become completely worn out, a climax is reached and the desire to do something to put an end to it all becomes urgent. Unfortunately, that something is frequently the removal of the child from the breast. The difficulty in getting him to take it properly and the commonly coincident dyspepsia, combined perhaps with the kind advice of friends and relatives, induce the idea that it is something the matter with the milk that is responsible for it all. So the breast-milk, already dwindling, is allowed to go, and a bottle is substituted. The effect is often dramatic. Belief in the success of her experiment restores the mother's confidence, and thereby also the child's good humour. The bottle is easier

to administer, and the child enjoys the readier flow of milk. Very often the screaming ceases and calm pervades the household. But peace has been bought at a price, the loss of the only food that is really adapted to the child's needs and his digestive powers.

These cases begin in one or the other of two ways. In one the anxiety comes first and the dyspepsia is only secondary. The mothers in this kind are generally young, primiparæ, devoted to their child, "good mothers" in fact, and they err through too much solicitude. (In one case, however, we believed that it was not an over-zealous care at all, but an irritable temper that was at the root of it. This child was the third, and it seemed from the mother's way of handling it that it was more an exasperation than a blessing.) However, the sequence of events is the same, namely nervous unrest, dyspepsia, increased unrest, increased dyspepsia, failure of breast. In the other kind the mother begins by making some grave mistake in management, then follow dyspepsia, anxiety, unrest, aggravation of dyspepsia, and finally failure of the breast. There is a difference of practical importance in the two, since the second type is easier to treat ; for if proper feeding is insisted on, the dyspepsia clears up, and with it the unrest. For the first, much more than this is needed.

The actual causes of the despepsia are, I believe, twofold. The first is the stimulation of the movements of the intestines by emotion, and the second is the mechanical derangement of the gastric functions by disordered suction. The effects of the emotions of anxiety and distress on the gut are the same in a child as in an adult, namely, increased peristalsis, and more frequent and copious evacuation of the bowels. The fæces of the over-stimulated, nervous child are apt to be more watery, bulkier and passed more often than those of the normal. This may give rise to the idea that the child is dyspeptic from over-feeding, whereas this may not really be the case. Indeed, irritable children actually require more food than placid children of equal bulk, on account of their continued muscular activity.

The effect of the disordered suction is that the child swallows a great quantity of air. In normal feeding the action of sucking is steady and rhythmical, but in the nervous infant it is rapid, irregular, and always liable to interruption. Moreover, he is always in a hurry, and attempts to gulp down his meal with violent and more or less inco-ordinate acts of suction. Very soon he has distended his stomach and refuses to take more, and perhaps begins to cry. Attempts to feed further are either resisted or result in further swallowing of air, and so a formidable obstacle to successful breast-feeding is produced. Naturally the mother attributes it all to defects in the breast-milk. But the reality of it can easily be shown by radiographic examination of the stomach. Where a child feeds normally the stomach is practically empty of gas, and even during the meal only contains a small bubble. The figure shows the stomach in cases of nervous unrest 5 minutes after a feed. An enormous gas bubble is seen occupying the stomach, and some of the gas is even passing on into the duodenum. Of course, this gas in the stomach is afterwards regurgitated ; but when the large quantity of it distending the stomach is presented to us

pictorially, we can easily see how great must be the difficulty the child has in feeding.

Fig. 2.—Radiogram of stomach of nervous infant taken five minutes after feed : stomach is distended with swallowed air.

Nervous unrest, therefore, presents itself to us as a condition in which besides a great deal of mismanagement, there is an actual mechanical derangement of the gastric function, which in its turn produces such a dyspepsia and loss of appetite that suction is seriously interfered with. It is therefore included among Diseases of the Child, with failure of the suction-stimulus as the actual decisive factor in the failure of the breast-milk.

Age Incidence. The average age at which weaning occurred was 11 weeks, varying from 8 up to 19 weeks. This seems rather later than experience would suggest. But the explanation is that these mothers were mostly heroic souls who tried hard for weeks to unravel the tangle of screaming and dyspepsia. The feeble ones who gave up early, did not attend regularly and so were lost to observation and not recorded.

Analysis.

Still keeping the cases divided into Controlled and Uncontrolled we can now show how many cases there are out of 115 in which the loss of breast-milk was a true failure of lactation, in how many it was not a true failure though controlled; and again in how many it was due to uncontrolled factors such as accident or mismanagement.

A. *Controlled—True Failures of Lactation.*

47 cases, or 40·9 %

Due to Disease of Child	17 cases	38
Due to Nervous Unrest	21 ,,	
Due to Disease of Breast or Nipple ..	2 ,,	
Due to General Maternal Ill-health ..	7 ,,	

One fact stands out clearly here: it is failure of the suction-apparatus that is the commonest fault. In all the 17 due to disease of the child this was the cause. So also in the 2 of retracted and deformed nipples. Then again diseases of the child are a commoner cause than disease of the mother. Mothers will repeat over and over again that it is their poor health that is responsible for their failure to nurse their babies. But it is, in fact, quite an uncommon event for the milk to fail for this reason: only in 7 out of 115 in this series. But the reverse is well known to hold good: namely, that the breast-milk will persist in spite of cachexias like anæmia, or severe infections like scarlet fever, or deadly disease like cancer. One is tempted to suppose that this is a device of nature, mindful ever of the future generation.

B. *Controlled—Not True Failures of Lactation.* (11 cases, 9·5%) comprising:—

Maternal Diseases	11 cases.

Most of the total number of Maternal cases were seen not to be true failures of lactation on examination. They were mostly the result of some mismanagement, or of the pain of a cracked nipple.

C. *Uncontrolled—Not True Failures of Lactation.* (56 cases, 48·7%), comprising:—

Mismanagement	27 cases
External Causes	30 ,,

These constitute practically half the total, and there is not a single one where normal breast-feeding could not have taken place.

D. *Uncontrolled—True Failure of Lactation.* (1 case, ·9%), namely, where the mother died.

The figures are too small for percentages to be of any statistical value, but they serve to give an idea of how small is the proportion of true failures out of the whole.

Conclusions.

1. A true failure of lactation is a relatively uncommon event. It occurs in less than half of all cases seen. It is due to abnormality or disease in either mother or child.

2. Disease of the child is the more important of the two causes of true failure. It occurs in the first few weeks of life, and this teaches us that where the breast fails early, we should examine the child first for the cause of the failure.

3. Interference with the suction-stimulus is the important basis of the failure of lactation. Disease of the suction-apparatis is therefore the usual underlying cause, either in the child's mouth, or his nose or respiratory system, or in the nipple or breast itself. There are a few cases also in which the child was too feeble to suck properly, either from prematurity or inherited disease or similar cause.

4. Maternal ill-health is a much less effective cause of true failure of lactation. It is widely stressed in books, it is obtrusively advertised on the hoarding by the proprietors of patent foods, and it is firmly believed in by the mothers themselves. But in reality it is rare. Exhaustion, starvation and unhealthy occupation comprise our seven cases. And how often do these conditions remain to-day ? Not often. And even when they do, more often than not the breasts still continue to secrete normally, I believe. It would be worth a little propaganda to implant firmly into the feminine mind that the mother's health has little to do with breast-feeding and that the child's is the all-important question. If the breast-feeding is not satisfactory, it is on the child that attention should be focussed. If the mother fails to carry out her functions, and then blames her own health, the chances are that it is her own fault that she failed.

5. Nervous unrest is a very common cause of failure. Interference with suction is shown to be the basis of failure. Mismanagement in the first place, however, is partly responsible. It is lack of experience in handling children, misunderstanding the functions of a mother, lack of insight into a child's need for rest and quiet, perpetual worry and fussing that often start the unrest. All these are faults that sound advice and education ought to eradicate. Then the interference with the suction-stimulus would not arise. There is also a miscellaneous collection of cases in which some disease or ill-health of the mother was the starting point, but in them the breast-milk ought to have been recovered or never lost, if they had been properly managed (at least, in our opinion). With better training of the mothers and more opportunities for continued and systematic observation, the numbers of failures in these conditions would have been much fewer. In nervous unrest, it is more education in the management of infants that is wanted to reduce the number of failures.

6. Practically half the cases of failure to breast-feed are not due to a failure of the function at all, but simply to mismanagement or to the interference of some outside influence. Or to look at it another way, even in a Welfare Centre where a special effort is made to secure breast-feeding half the

cases of failure to breast-feed need never have arisen, and contain no obstacle to recovery except ignorance, prejudice, interference and similar causes. In practically all these again breast-feeding would have gone on normally if the friendly cow or the tin of condensed milk had not been at hand.

7. We are left then with the conclusion that half the cases need not have arisen, and that well under half are genuine. If we regard nervous unrest as a condition that ought to be overcome, then only a quarter appear inevitable. We should, therefore, always try to insist on breast-feeding. In nearly every case it can be done, if only we can give it time and trouble enough. No mother should be encouraged for an instant to believe that she could ever be likely to fail with it, except because of a cleft palate in the child, or some such palpable defect. No interference with it by supplementary feeding should be allowed except on the advice of those who understand the manifold dangers of such interference. Even then it should not be undertaken unless it is known to be absolutely necessary, by investigation, and should be controlled when instituted by further investigation with a view to subsequent abolition if possible. It might seem almost superfluous to say this, if one did not know how seldom it is carried out. How often, for instance, does one come upon children whose mothers have been light-heartedly advised to give them a bottle merely because of some slight deflection of the weight-curve or other trivial reason, or have been told that they are " not strong enough " to feed the child, or that their " milk does not agree," when all the time the child is suffering from dyspepsia from being grossly overfed ! All such harmful ideas are without foundation in almost every case, and they should be obliterated from the maternal mind. Instead the idea should be inseminated that breast-feeding is easy if a very few simple rules are carried out, and that it hardly ever fails ; and further that artificial feeding should only be undertaken with reluctance and under strong compulsion.

8. Finally, where cases of difficulty in breast-feeding are likely to occur, there should be opportunities for manifold test-feeding, and, if possible, for observation during and between the feeds.

CHOLÆMIA.

A Clinical Study of the Nervous Symptoms in Liver Atrophy.

BY

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The idea of a relationship between diseases of the liver and nervous symptoms is long established, as is suggested by the origin and use of the adjective ' choleric.' Wilson's discovery of a group of cases in which cirrhosis of the liver is associated with progressive degeneration of the lenticular nucleus of the brain and striking nervous symptoms, received the immediate attention it deserved, largely because it offered concrete pathological evidence of this relationship. Apart from these we have evidence of the characteristic feelings of depression of a jaundiced patient, and the acute nervous symptoms which may usher in the terminal, or so-called cholæmic, stage of acute liver diseases. Comparatively little has been written on these cases, so that certain observations we have made appear to us worthy of record. These are concerned with nervous signs and symptoms which occurred in two recent cases of liver atrophy in children, and they have been augmented by reference to the clinical records of nineteen other cases of acute or subacute liver atrophy which have come to post-mortem examination in this Hospital since 1913. Of these 21 cases only five were children of the ages, 4, 9, 10, 11 and 14 years. But the subject has a special interest for students of children's diseases because of the greater intensity of the clinical picture in childhood and the resemblance it may bear to that of meningitis.

The first two cases we describe offered good opportunities for the study of the nervous signs, as they ran their courses without the intervention of any terminal complication such as pneumonia or peritonitis to alter the clinical picture. One of the most striking features was the peculiar type of noisy delirium they exhibited. It was more than mere febrile delirium, the peculiar wailing and crying being unlike anything else we have seen in other toxic or delirious states. So distinctive are they that they almost merit the description of ' cholæmic cries.' The first case had an extensor plantar response on one side only, and it would appear that there was also some paralysis of the muscles of accommodation in the eyes. The second case had a paralytic squint. He had also nasal speech and palatal paralysis resembling diphtheritic palsy, yet in the absence of any evidence that it was diphtheritic in origin : a point to be noted, for we shall refer to a case of Bright's described in 1836, which appears to have shown the same disability. Another point to be noted, although its significance cannot be explained, is that the first case had a typical duodenal ulcer, a rare event in a boy of nine.

Case 1. Boy aged 9 years. Admitted 19.4.26. Died 22.4.26. A very accurate and detailed history was obtained from Dr. Charles, who referred the case to hospital as follows :— A perfectly healthy active boy up to onset of illness 3 weeks before admission. Member of a healthy family with no evidence of syphilis. The first symptoms were lassitude and drowsiness, with some vomiting in the first week. During the second week he was easily tired and peculiarly lethargic and drowsy, and the possibility of encephalitis or meningitis was considered. There were nausea and occasional vomiting with some slight abdominal pain and an attack of diarrhœa for a few days. At this stage his eyesight appears to have become affected in a peculiar way. He was not yet acutely ill, being able to sit about at the fireside, and he is described as being " unable to see things properly and groping for his food at table." In the third week he became worse and took to his bed. Two days before admission (17.4.26) he was obviously dangerously ill with swollen abdomen, œdema of the feet and delirium. At this time there was no jaundice, and the urine contained no albumen or sugar.

On admission on 19.4.26 the boy was extremely ill and restless. Pulse 112. Respirations 24. Temperature normal. There was obvious recent loss of subcutaneous fat. There was considerable ascites, and the liver was smaller than normal though the edge of the left lobe could be felt high up in the epigastrium and was very hard. Spleen enlarged. The heart and lungs showed nothing to account for the illness. The urine was acid, 1025, no albumen and contained a trace of sugar. Cerebro-spinal fluid was normal. Blood urea 40 mgms. per 100 c.c. No jaundice or petechiæ present. Occult blood was present in the stools.

On this day the nervous signs were as follows :—He was in a restless state suggesting at first sight tuberculous meningitis, but differing from that in the way he would sit up apparently quite conscious, giving vent to peculiar wails and piercing shrieks, refusing to be comforted. These were not mere complaints of acute pain or the insensate cries of semi-coma. They went on at times for as long as ten or fifteen minutes while he sat up in the corner of his cot, resembling some terror stricken animal in its cage. He would then subside into quieter states of irritability or restlessness, to be followed again by these attacks of active shrieking and plaintive wailing. The pupils were widely dilated, but reacted to light. As far as could be seen there was no reaction to accommodation and the fundi oculi were normal. No squints or ptosis. Both knee-jerks and ankle-jerks were present. On the right side there was a well-marked extensor plantar response, on the left side it was equivocal. There was no stiffness of the neck. During the next three days before death the extensor response on the right side persisted, the left plantar response remained indefinite. Pupils remained widely dilated. The restless state continued, but now the periods of crying and wailing were varied by the intermission of convulsive attacks in which he held himself in a position of opisthotonos, the attacks lasting perhaps half a minute and severe enough to suggest poisoning by strychnine. When these passed, there was no rigidity and no neck stiffness, and he lay for the most part quiet and flaccid with occasional return of the 'cholæmic crying.' At this stage the Ward Sister ventured the opinion that in spite of the obvious resemblance to meningitis, she had never seen a case of meningitis behave as this case, in the way he changed from one state to another, nor had she ever heard such peculiar wailing going on as it did at intervals for two days and nights. On 22.4.26 petechiæ appeared on the arms and trunk. He vomited blood, then sank into a weak comatose state and died. Jaundice, though eagerly sought for, was absent throughout the illness until 24 hours before death when it appeared in the conjunctiva. Blood taken for a Van den Bergh test on the last day gave a direct positive reaction. A trace of sugar was present in the urine until the last day.

Post-Mortem examination (*by Dr. A. F. B. Shaw*) : A slight degree of jaundice could be noticed in the conjunctiva and skin. A typical condition of advanced subacute atrophy of the liver was found. The liver weighed 28 ozs. Capsule wrinkled in places. Small areas of nodular hyperplasia, canary yellow in colour, varying in size. Spleen enlarged. Ascites present. Small hæmorrhages on surface of heart, at the cardiac end of the stomach and along the small intestine at the mesenteric junction. The pleural and pericardial cavities contained a few ounces of bile-stained fluid. The heart, lungs, kidneys, suprarenals, and pancreas showed nothing of note. The brain was carefully examined and there was no evidence either naked eye or histological to

account for the nervous signs and symptoms. The stomach and intestines contained altered blood. There were no inflammatory lesions in the bowel. There remains to be described the duodenal ulcer already referred to. This was a typical elliptical peptic ulcer one inch in breadth on the first part of the duodenum; the edges clean cut and vertical; the floor smooth and fibrous. There was no eroded vessel to be seen in the floor.

In the next case it is to be noted that the terminal cholæmic state was ushered in by the same type of wailing and 'cholæmic crying' as in the first case. The resemblance was remarkable and of sufficient significance to enable a clear definition of the prognosis.

Case 2. Boy aged 4. Admitted 22.4.26, died 27.4.26. *History:* The boy had been vaguely 'out of sorts' for 4 months before admission to Hospital. The only definite illnesses had been tonsillitis 9 months and again 5 months before admission, for which the operation of tonsillectomy was performed 10 weeks before admission. From this he made a good recovery, the throat being free from any apparent diphtheritic infection during the stage of recovery. Three weeks before admission he developed jaundice with vomiting and clay-coloured stools. At the end of the second week he began to recover from this and was 'out and running about' two days before admission to Hospital. Next day he became ill again with weakness and lethargy and he was referred for admission to hospital.

On admission. Temperature and respiration normal. Pulse 120. Looked ill and toxic. Quite conscious and able to respond to instructions, but a tendency to drowsiness. Deeply jaundiced. Liver: no alteration in size, firm edge felt just below costal margin. Spleen not enlarged. No ascites. The chief nervous signs at this stage were as follows:—Pupils widely dilated and unequal, right larger than the left. Both react to light. Paresis of the right external rectus with internal squint. No ptosis. Very distinct nasal speech with palatal paralysis. Other cranial nerves normal. Both knee-jerks absent. Both ankle jerks present but responses very faint. Both plantar responses definitely flexor. There was no neck rigidity. Swabs were taken from the nasopharynx and throat. No K.L.B. found. Blood urea normal (28 mgms.). Blood sugar raised = 0.226%. Urine contained a trace of sugar, bile, acetone, and diacetic acid. Leucin or tyrosin were not found. At this stage a diagnosis of catarrhal jaundice was made, but no explanation could be given for throat and eye symptoms.

Two days after admission (*i.e.*, three days before death), the condition changed rapidly for the worse. He became extremely restless and the peculiar 'cholæmic crying' noted in the first case commenced. He preferred to sit up in bed wailing and shrieking intermittently. There appeared to be some photophobia at this time. This state continued for two days, quite conscious sleeping, at intervals, but generally miserable and refusing to be comforted. For these two days the shrieking and crying continued loud enough to be heard in other parts of the hospital and requiring his removal to a side ward. Twenty-four hours before death the picture changed again. He began to sink into coma, and fits commenced, differing a little from the convulsive attacks seen in the first case. In these he threw himself across the bed with his arms above his head and eyes wide open. There was no definite rigidity in these attacks. The lower jaw was flaccid and there was no neck rigidity. During these attacks urine was passed involuntarily. Intermittently the crying continued in a weaker plaintive tone. He died in deep coma.

While under observation the plantar responses remained definitely flexor. Slight glycosuria persisted until the last two days when insulin and glucose treatment was instituted as an attempt to combat the acidosis. The temperature remained normal or subnormal throughout. The pulse rate which was 120 on admission advanced as the illness progressed.

The *post-mortem* was done 2 hours after death by Dr. A. F. B. Shaw. The findings were those of typical liver atrophy. Weight of the liver 18½ ozs. The surface of the liver consisted in some parts of slightly raised yellowish-green tissue, in others of depressed areas dull red in colour. The quadrate lobe was large and appeared to be composed entirely of regenerated liver tissue. On section the organ was typically greenish-yellow in colour cutting firmly, the appearances being those of a subacute atrophy of the liver. Naso-pharynx was clean without

evidence of diphtheritic membrane. Small hæmorrhages were present beneath the surfaces of the lungs and in the mesentery. There were some actively caseous glands in the omentum. Otherwise all other organs shewed no special change. The liver condition was confirmed by microscopic examination.

Duration of Symptoms.

The clinical records of the remaining 19 cases are not complete enough to allow a full comparison of all the details of the nervous signs and symptoms noted in the two cases we have described, as some of the patients were admitted to hospital within a few hours of death. In one the picture was complicated by a terminal rupture of a duodenal ulcer, and in three others by extensive bleeding from the bowel. But when the nervous symptoms had been observed and noted, the chief feature commented on was the supervention of 'noisy delirium,' 'shouting' or 'extreme restlessness' a short time before death. The most frequent sequence of events was a stage of drowsiness or lethargy followed by a period of noisy delirium, and ending in coma. Out of the total 21 cases this sequence, or some slight variation of it, could be traced in 16, including the 5 children.

The duration of the acute nervous symptoms of the terminal phase varied in these cases from 12 days to one day, with an average of 4 days. But this period was difficult to define, for in some cases of the subacute type a history was obtained of transient attacks of coma or drowsiness for several weeks before death. This is exemplified in the following instance of a man who died with typical subacute liver atrophy, who had recurring attacks of coma off and on for 6 weeks before death.

Case 3. Man aged 35. Admitted 22.3.22; died 1.4.22. History of syphilis and salvarsan injections in 1919. The first symptoms appeared seven weeks before death with swelling of the abdomen and jaundice. A week later he had an attack in which he was drowsy and then comatose for 24 hours, followed by complete recovery of consciousness. A week or two after a second attack of coma occurred lasting two days, and again from this he recovered. During these attacks he could not be roused and there was loss of sphincter control. Admitted 9 days before death there were no nervous symptoms or signs. Two days later he had an attack (the abdomen had been tapped a few hours before) in which he is described as "very noisy for an hour or two, shouting and crying, and with incontinence of urine and fæces." He recovered temporarily from this and later became unconscious and died.

Although the appearance of coma or noisy delirium usually denotes the approach of the terminal stage of the disease, we feel that it is neither necessary nor profitable to attempt to define them too closely as a ready means of foretelling the issue. Stuart M'Donald and Milne[1], in a study of the pathological changes in subacute atrophy of the liver have commented on the difficulty of estimating the duration of the morbid processes. They describe cases in which they judged the liver changes to have been present for varying periods up to 7 months. The same difficulty exists in attempting to assess the significance of some of the vague symptoms such as lassitude and sleepiness which some of the cases show for several months before more definite evidence of liver disease show themselves. Moreover this difficulty is presented more clearly

when we remember that all studies of subacute or acute liver atrophy are based on cases which ultimately die. It seems to be tacitly understood that such a diagnosis is ventured only when the liver disturbances, or jaundice if it be present, are severe enough to kill the patient. Short of that, or if recovery takes place, the diagnosis of catarrhal jaundice or perhaps "acidosis" is given. Apropos of this we have recently heard of a case of which we are not able to give full details, in which the patient had symptoms suggesting encephalitis from which he recovered. For the next six months he had vague abdominal and digestive trouble for which a laparotomy was done. At the operation a 'cirrhotic condition of the liver' was found. This may be a case in which acute or subacute atrophy of the liver was present at the time of the encephalitic symptoms of lethargy and from which a recovery was made to go on later to cirrhosis. Byrom Bramwell's[2] suggestion that certain unusual cases of cirrhosis in young people might be a phase of Wilson's disease in which the nervous manifestations had not yet declared themselves, has a bearing on this point.

Summary of Observations.

Without giving details of the other three cases in children and of the remaining adult cases, some points of interest in the whole series of 21 cases can be summarised for brief discussion.

Of 21 cases of liver atrophy 5 were children of 14 or under. These were traced from a total number of 4958 post-mortems in a period of 13 years, and thus represent only the fatal cases which occurred in this time. The possibility exists that other cases have occurred and have recovered.

The pathological changes in the liver in these cases were as follows: 1 case of acute atrophy (acute yellow atrophy) and 20 cases of subacute yellow atrophy. Or classifying them in the way that Miller and Rutherford[3] suggest, in which the subacute group is further subdivided according to the amount of regenerative changes found in the liver: 1 case of acute atrophy with early fibrosis, 5 cases of subacute atrophy with early fibrosis, 15 cases of subacute atrophy with marked nodular hyperplasia.

In all 5 cases of children, and in 11 of the adult cases a certain sequence of nervous symptoms characterised the terminal or 'cholæmic' stage. This was more evident in the children than in the adults and consisted of lethargy or stupor, a period of unusual shrieking and crying, a stage of convulsions, death in coma.

The most characteristic of these stages of nervous symptoms was that of maniacal shrieking and wailing which we have termed 'cholæmic crying.' It was not present in all cases, but when it occurred it was distinctive, differing from mere toxic delirium.

In 8 cases where a systematic examination of the reflexes was recorded extensor plantar responses were present in 3. In one of these it was unilateral.

In one case there was palatal paralysis and nasal speech.

In one case there was a paralytic strabismus due to a 6th nerve paralysis.

In 4 cases cerebro-spinal fluids were examined. In none of these were there increases of cells or of protein.

Jaundice was present in all cases but varied greatly in degree, and the appearance of the nervous cholæmic symptoms can bear no relation to it, when we consider the features of the first case we have described. For there a slight tinge of jaundice appeared only in the last 24 hours, when the boy had already had acute nervous symptoms of cholæmia for 6 days. (We recognise from this the mistaken etymology of the term 'cholæmia' in the sense that we have used it. But the use of it as a clinical term to express the terminal stage is justifiable, just as 'uræmia' is used for the analogous toxic stage in kidney disease, although excess of urea in the blood is not the toxin concerned.)

In 4 of the cases of the subacute type with ascites and jaundice, the acute cholæmic stage was precipitated by tapping the abdomen to relieve abdominal discomfort.

A terminal pyrexia was noted in 5 cases, only two of which had bronchopneumonia. Thus the nervous symptoms of cholæmia cannot be explained by a sudden accession of fever.

In six cases there was evidence of syphilis and treatment by salvarsan, and in one other case of congenital syphilis without treatment by salvarsan. The clinical picture of the cholæmic stage in this group did not differ from that of the other cases.

Discussion.

A few of these points will need more discussion than the comment we have made on them.

Extensor plantar responses. It has long been established that these may occur in cholæmia. As far as we can find Rolleston[4] first drew attention to it in describing a case of acute yellow atrophy. Later Willcox in his Lettsomiam lectures[5] described cases of infective jaundice, and Elliott and Walshe[6] cases of hepatic cirrhosis, which developed extensor plantar responses in the terminal cholæmic stage. These are mentioned again by Walshe[7] in his review 'The Babinski plantar response in toxic states.' Elliott and Walshe state that the stage of cholæmia may be recognised "by the mental changes of mild delirium or drowsiness, associated with a double extensor response." This suggests that the extensor plantar response characterises the toxic stage of cholæmia and is a necessary sign or accompaniment of it, for they go on to state the converse that other cases of hepatic disease may sink "quietly and slowly to death without acute mental changes and without an extensor response even in the last hours, that is, without cholæmia." We agree that careful and repeated examinations of the plantar reflexes should be made in any suspected case, but we cannot agree that when cholæmia ensues, extensor responses will necessarily be found. In our first case it was present on the right side and indefinite on the left. But in the second the responses remained definitely flexor, for they were tested carefully and repeated by

up to the hour of death. Yet this case had the other classical symptoms of cholæmia; maniacal shrieking, jactitations and fits passing on to coma and death. We must therefore presume that although extensor responses may be a valuable physical sign of cholæmia, they are not necessarily present.

Palatal paralysis. This occurred with well defined nasal speech in one case. It was observed in the early stage for a day or two preceding the maniacal shouting, convulsions or coma, and the lack of movement of the palate was easily demonstrable. Its appearance may have been quite fortuitous in our case. We therefore hesitate to define it as a nervous sign of cholæmia : but on the other hand it may be so. In the case described there was no evidence of any other possible cause such as diphtheria. We have been unable to find any record of it in any previously reported case, unless it be a short note that Richard Bright[8] made on one of his cases. This was in 1836 in a paper which he wrote in the first volume of the Guy's Hospital Reports on ' Observations on Jaundice more particularly on that form which accompanies the diffused inflammation of the substance of the liver.' In this he describes graphically the clinical picture of the condition we now term acute liver atrophy. The note was made 6 days before death and reads : " She generally prefers the sitting posture in bed. Some sluggishness of speech and a plaintive tone."

Maniacal shouting and convulsions. The maniacal shouting (cholæmic crying) was more evident in the children than in the adults. They gave the appearance of suffering intense pain which they could not explain and it is of interest that we noted that when the shouting and crying went on they " preferred the sitting posture," as Bright describes it. As a reference to other descriptions of the noisiness, restlessness and convulsions we can do no better than quote further from Bright. Of one of his cases he writes : " She had all the appearance of a person sinking from the loss of blood, with constant and distressing jactitations, and delirious though faint exclamations. She continued delirious and sank in the afternoon of the following day." Of another : " Nov. 28th.—She generally prefers the sitting posture in bed. Some sluggishness in her mode of speech, and a plaintive tone. Dec. 1st.—Her pupils are rather dilated : her mode of utterance is dull and indistinct : complains of loss of power in the left hand : the right is already disabled by disease. Dec. 2nd.—Is lying on her right side, drowsy, with her legs drawn up, moving her left hand with a kind of jactitation. Dec. 3rd.—Yesterday evening she was screaming loudly, with her tongue protruded beyond her teeth. Today she is in a state of perfect coma with the eyes turned up." And of another : " She lay in a perfectly torpid state the whole night ; but towards the morning became delirious, so that it was with difficulty she could be restrained in her bed. At the time of the visit she was very restless, and seemed to suffer pain ; but was unable to answer questions."

Cause of Cholæmia. Of the ultimate cause of the toxic state in liver diseases which we term cholæmia, we can offer no explanation. It would appear that the phrase ' hepatic insufficiency ' is inadequate to do this. This implies

that a stage of destruction of liver tissue is reached when the hepatic functions fail altogether and toxæmia ensues. Following the results of the experimental Eck's fistula in animals in which convulsions ensued after administration of protein but not of carbohydrate or fat, it has been held that the symptoms of cholæmia are due to the passage of protein substances through the damaged liver that have not been de-aminised. In three of our cases only were estimations made of the blood urea or urine urea. These were carried out at the height of cholæmia and yet the percentage of urine urea reached 2·4% to 3·0% and the blood urea was normal. This hardly suggests a complete breakdown of the urea-forming function of the liver. Moreover, cholæmia may arise as readily in the subacute cases where rapid regeneration of liver tissue has taken place as in the acute cases with extensive destructive changes. The recent researches of Mann (9) and others at first sight suggest hypoglycæmia as the cause of the cholæmic convulsions. They found a progressive fall of blood-sugar, ending in convulsions and death, in dogs whose livers they had successfully extirpated. This explanation, however, will not serve in our first two cases. In both, traces of sugar were found in the urine, and in one the blood-sugar was high (0.226%). Another possible explanation that could be offered is the production of some autolytic poison from the liver substance itself at some stage or other of the pathological changes which it undergoes. This is suggested by a case which one of us saw six years ago. It was a boy with lymphadenoma whose enlarged cervical glands were being treated by X-rays. The glands began to decrease in size, but in the course of treatment he developed severe toxic symptoms which lasted 3 to 4 days, and resembled closely the picture we have drawn of cholæmia. This case was fully investigated at the time and a careful post-mortem examination made, but none of the usual causes of terminal toxæmia were found, and we were left to presume that the condition had resulted from the release of some autolytic toxin from the lymphadenomatous glands.

Our thanks are due to Professor Stuart M'Donald for the use of the pathological records and for help in re-examination of the microscopic slides of all these cases, to the members of the Honorary Staff of the Hospital whose clinical records we have used for this paper.

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THE USE OF BANANA PULP IN THE FEEDING OF MARASMIC INFANTS.

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The experience of all childrens' physicians in the feeding of marasmic infants is, I suppose, identical. It is not difficult to devise a method of feeding which shall be sufficient in quantity, and scientific in quality, and further is tolerable to the infant : but it is extremely difficult to secure that such a food shall be absorbed and built up into the tissues of the body. I am, of course, using the term marasmus in a strict sense to indicate that condition in which wasting disease is progressive or stationary without sufficient discoverable cause. In such cases it is, I believe, a common experience for the physician to find that in spite of his efforts to contrive a food which will benefit his patient, the condition remains unaltered for many weeks, with no gain in weight or strength, and yet with no appreciable lack of capacity in the digestion of the various foodstuffs of which trial is made. Further it is, I think not uncommon to find that such infants begin to put on weight, if their food contains an excess of carbohydrate material ; and it is probable that this factor is mainly responsible for the reputation of some of the proprietary foods which contain starch or starch-products in large quantity. Yet even with the use of such foods there is a proportion of marasmic infants, who steadily refuse to improve and are the despair of the physician and the nurse. It is with cases of this type that I have lately experimented with the use of ripe banana pulp to supply the excess of carbohydrate which seems to be required, and the sudden and to me the unexpected improvement appears to be worth recording.

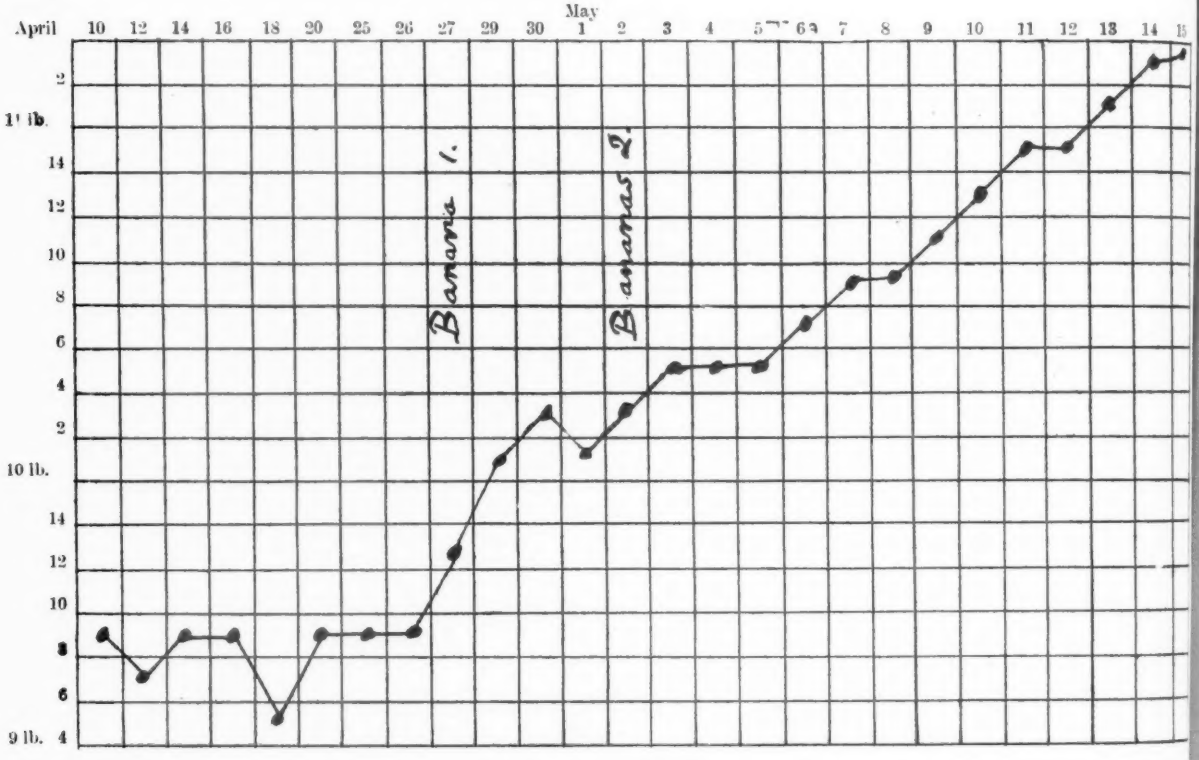
The cases to which I shall refer are six in number ; four of the true marasmic type, and two " ruminators."

The first patient was admitted to the Hospital at the age of three months weighing about ten pounds. He had had a convulsion at the age of six weeks and since then had suffered from intermittent vomiting and failure to progress. In the ward the vomiting soon ceased but at the end of ten weeks in the Hospital he had made no gain in weight and actually weighed rather less than on admission. He was at this time on a diet which consisted of cows' milk, whey and Benger's Food. This had a calorie value of 580 C. per diem and was readily taken and retained and apparently well digested. Of the 580 C. roughly 300 were carbohydrate, 200 fat, and the remainder protein. At this point he was given the pulp of one ripe banana per diem and a few days later the Benger's food was omitted and on May 1st his diet was merely cows' milk and the pulp of two bananas with a calorie value of about 590 C. A reference

to the chart will show that the weight had already taken an upward turn. The pulp of a second banana was added and shortly it was possible to increase the amount of milk, an increase which had always previously been attended by indigestion and loss of weight. He was discharged from the Hospital three weeks after he had begun the banana diet on a diet of about 700 C. of which 100 C. were banana-carbohydrate calories.

CHART I.

G.H. 3/12. Admitted 20.XI.25. From date of admission to 10.IV.26, no gain in weight.



I have gone somewhat into detail in this case so that I shall not need to repeat the minuter details in other instances. The point which I wish to emphasise is that the addition of the banana pulp to the diet did not increase, but in fact slightly diminished, his total carbohydrate intake, though it maintained it at a point considerably above the normal proportion found in cows' milk: that is, that the good effects must not be attributed to added carbohydrate, but rather to the special form in which this was given, *i.e.*, the banana pulp.

The second, third and fourth charts exhibit the same phenomenon, though in an even more marked degree. The addition of banana pulp to the diet, replacing some of the carbohydrate previously given in another form, had the effect of increasing the weight and general well-being almost at once. I must here add that the change in the general condition must be seen to be appreciated at its proper value: from puling unsatisfactory infants they quickly became smiling and contented children. When once improvement has begun the amount of food which can be taken and utilised is rapidly increased. In the first case the increase in weight took place without any marked addition to the actual amount consumed, but in some of the other cases after the increase had begun with an unchanged amount of milk, this could be augmented rapidly without any fear of indigestion, whereas the previous attempts to increase the intake had invariably failed for this reason. This feature was especially noticeable in the patient whose progress is recorded

CHART II.

C.C. Aged 9/12. Admitted 17.ii.25.

From admission to April 14, no gain in weight.

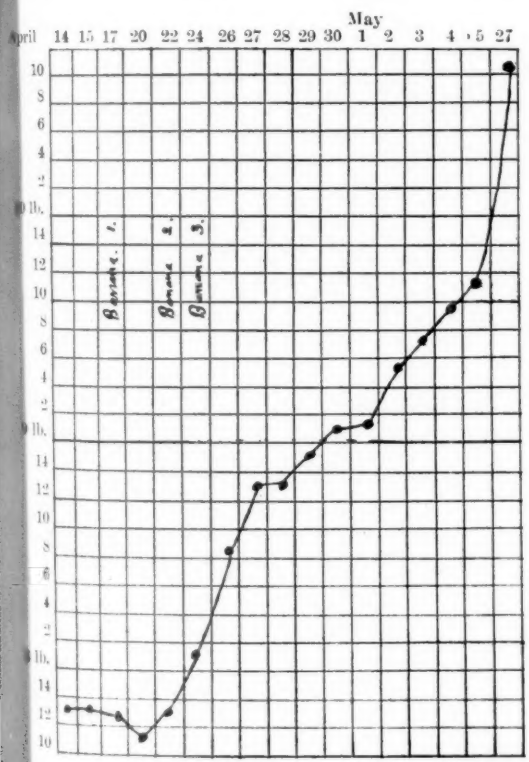
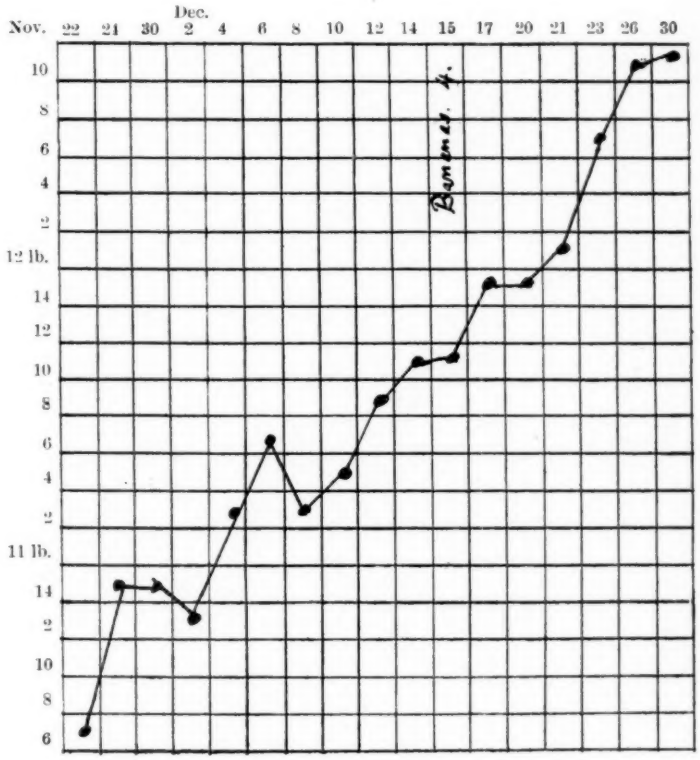


CHART III.

M.B. 4/12. Admitted 23.IX.24.

Weight stationary till Nov. 22nd.

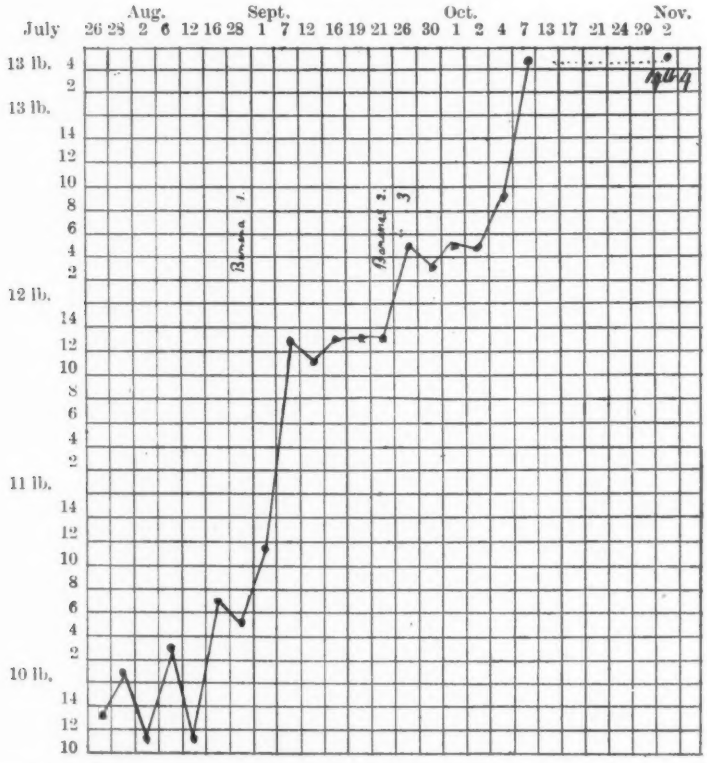


in Chart IV. Repeated attempts had been made to increase the amount of intake and each attempt had been followed by a set-back due to indigestion. When once the improvement had been initiated by the use of the banana pulp

CHART IV.

T.W. 7/12. Admitted 9.VII.26.

No gain in weight.



it was possible to add milk in considerable quantity to her diet, and eventually rusks, green vegetable and gravy. The same thing was observed in the case of the older of the two "ruminators." In the younger the increase in weight took place without any addition to the total calorie value of the diet. These two "ruminating" cases belong to a slightly different category than that of the other infants. They are marasmic infants, but there is an appreciable cause for their steady refusal to put on weight, in the "rumination" and rejection of some portion of the food which they have actually swallowed. Yet in both cases the addition of the banana pulp was the first step in solving the problem of the feeding.

To sum up the facts here recorded: six infants in whom the prolonged efforts of the physician, his house-physicians, and the Sister, had entirely failed to produce any improvement in power of absorption and utilisation of food, with the addition of comparatively small quantities of banana pulp at once began to make headway.

Naturally the question arises as to the property in the pulp which is apt to produce such welcome results. The actual facts regarding the composition of the banana are as follows: Of 100 grammes of ripe banana pulp approx-

CHART V.

D.S. 1/12. Admitted 21.x.24. Ruminator. Weight stationary from August to December.

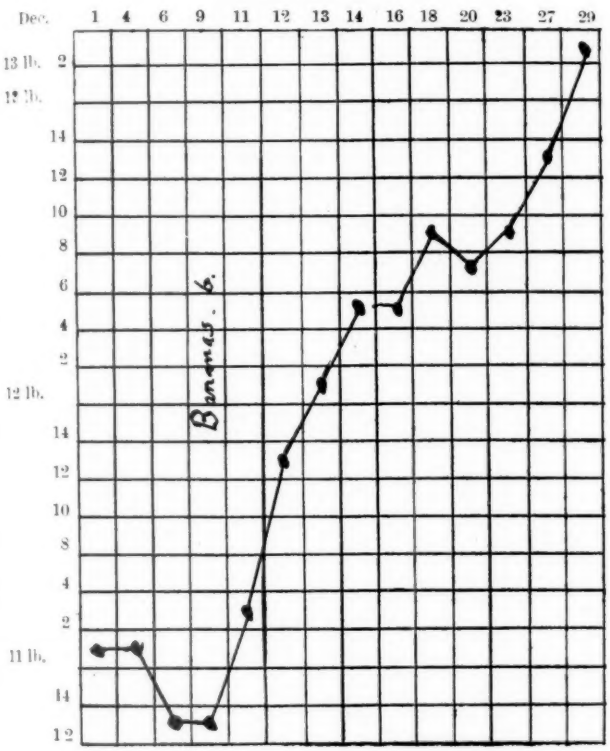
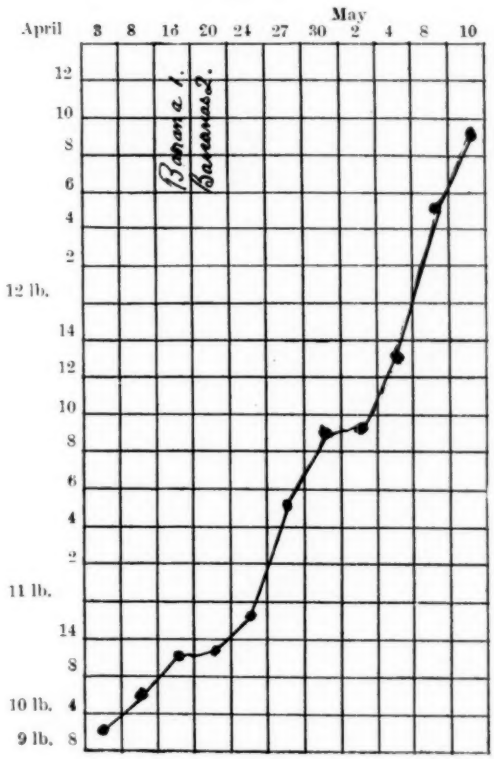


CHART VI.

F.G. 8/12. Admitted 2.IV.25. Ruminator.



imately 70 are water; about 1·5 grm. are fibre, which is mainly discarded in the method of preparation which has been employed: and from 21 to 27 grm. represent starch or sugar. There is practically no fat, less than 0·1 grm. per cent. and protein is about half of one per cent. Ripe banana pulp prepared as will presently be described, may be considered to have a food-calorie value of 85-100 C. per 100 grammes. The average weight of one stripped banana varies from 50-70 grammes. In addition, bananas have a certain, not a high, anti-scorbutic content, and contain water-soluble B. Their content of fat-soluble A is negligible.

I think it may safely be concluded that the results are not due to any of these vitamines. In all the cases recorded fresh orange-juice had been given

in ample quantity during the whole of the 'pre-banana' period. It certainly cannot be contended that it is due to the mere addition of carbohydrate because sometimes, as in the first case, the total carbohydrate intake was actually diminished when the banana pulp was added.

Nor can the nature of the carbohydrate account for the effects produced. In a ripe banana the starch has been converted into various sugars, chiefly, it would appear, maltose and glucose, with a small proportion of saccharose: that is, broadly speaking, sugars identical with those present in the malted foods such as Benger's.

The method which we have used in preparing the banana pulps is as follows: A ripe banana with as few bruises as possible is selected, stripped and any bruised portion cut away. The obvious fibres are removed and the remainder is pulped with a fork and then strained through coarse-meshed muslin so that the fibrous portions remain behind. The resulting pulp is mixed with the milk in the proportions ordered in one or several feeds; the pulp of one average banana being considered to have a calorie value of roughly 50 C. The teat used for the bottle has an aperture rather larger than usual.

A further point which should be noted is that the stools of infants on the pulp present a characteristic appearance; small black particles which represent the fibre which has passed through the sieving process are so abundant as to give the stool a stippled appearance.

SUMMARY.

An account is given of a method of feeding 'difficult' infants with banana pulp.

It is claimed that by this method in many cases progress is secured which is superior to that obtained by other methods.

It is suggested that the benefit is due not to any known peculiarity of the banana as a food, but possibly to some unidentified element in the banana. I may add that Dr. Harrison investigated this point for me without discovering any new element.

KETONÆMIA, CYCLICAL VOMITING AND SOME NERVOUS DISTURBANCES IN CHILDREN.

BY

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**An Abstract of an address delivered at the James Mackenzie Institute, St. Andrew's.*

Ketonæmia and Hypoglycæmia.

In 1911 Frew[1] drew attention to the great frequency of ketonuria in the children recently admitted to the wards of The Hospital for Sick Children, Great Ormond Street. All clinical experience and all experimental work are in accord in recognizing that a significant ketonæmia occurs more readily in childhood than in adult life. The extensive literature concerning ketonæmia and ketonuria in children has been recently reviewed in the *Archives of Disease in Childhood* by Brown and Graham[2] as an introduction to their own admirable work on the subject.

Acetone bodies commonly appear in the breath and in the urine of children (*a*) during infection marked by considerable pyrexia ; (*b*) during fasting (*c*) during vomiting of such persistence and severity as to interfere with the intake of food ; (*d*) after anæsthesia, and (*e*) upon a diet containing a great deal of fat and little carbohydrate.

Coincidently with the rise in the amount of ketone bodies and with the corresponding fall in the alkaline reserves of the blood many observers have found a considerable fall in the percentage of blood sugar. Thus whereas in adults the blood sugar remains remarkably constant despite prolonged starvation, in children it would appear that there may be a considerable though sometimes shortlived fall and that in general the younger the child the more severe the fall. In a study of the metabolism of young children subjected to prolonged periods of fasting Shaw and Moriarty [3] found that the ketosis, the fall in the plasma bicarbonate and the hypoglycæmia were all on a much greater scale than in adult life. There was indeed a definite fall in the *p*H value of the blood. In the later days of the fast some degree of compensation was achieved and the sugar content became less depressed. The depletion of the glycogen reserves would appear to occur more rapidly in fasting children than in fasting adults and the body appears unable for some time to bring about a glucose synthesis sufficient to maintain a normal blood sugar.

Upon children actually subject to cyclical vomiting as yet comparatively little work has been done. Hilliger [4] in 1914 first detected a fall from 0·14 to 0·07 in the blood sugar in a child with cyclical vomiting accompanying the development of the ketosis. In a young child two and a half years old, the subject of typical attacks of cyclical vomiting, Ross, Hughes and Josephs [5] found a fall in the blood sugar and of the CO2 combining power of the blood, but noted that the recovery was so rapid that the hypoglycæmia could only be demonstrated during the height of the attack.

Wilson, Levine and Rivkin[6] investigated the oxidisation of the food stuff in a suitable group of six children one of whom suffered from cyclical vomiting. They found that children do not necessarily oxidise food stuffs in the proportion ingested, a circumstance which renders dietary data unreliable. Normal children usually oxidise a higher proportion of carbohydrate and a lower proportion of fat than they receive in their diet. The difference is most marked when the fat intake is relatively high. In the one child with cyclical vomiting this replacement of fat by carbohydrate derived from the stores of the body was much less obvious. The authors suggest that while normal children are by preference carbohydrate burners, readily replacing any excess of fat in the ingested mixture by carbohydrate, this power of adjustment is less developed in cases of cyclical vomiting. The subjects of this disorder are pronounced fat burners. If fat in excess of carbohydrate is provided, an attempt is made to oxidise all the fat and the necessary additional carbohydrate is not mobilised from the stores of the body. This pecularity, it is suggested, may be the factor which explains the great ketonæmia in cyclical vomiting. Observations on this point are too few at present to permit any quantitative statement. The lower carbohydrate utilisation in the one child with cyclical vomiting was shown in a subsequent paper by the same authors, not to proceed from any diminution in the power of storage of glycogen. In the same child too, between attacks and in the resting condition, the quantity of carbohydrate mobilised from fully replenished stores and oxidised during short periods of fasting was not diminished below the normal. Recently, Haldane[7] and others have shown that changes in the acid-base balance can profoundly influence carbohydrate metabolism. It is possible that in predisposed children the ketonæmia may have secondary results of this nature.

The Characteristics of the Child with Cyclical Vomiting.

Further investigations in this direction upon the metabolism of normal children and of children with cyclical vomiting are needed before we can have complete understanding of a variety of very common disturbances of health in young children. Nevertheless, what has been already accomplished, although it touches but the fringe of the subject, is so suggestive that it may be profitable to review our clinical studies and concepts in the light of these new findings.

As has been said, all children, just because they are children, respond to a variety of stresses—to infection, to excitement, to over exertion, or to starvation —by the development of ketonæmia. In the child prone to Cyclical Vomiting it is clear that this response is of maximal intensity. Such children, often if not invariably, have certain temperamental and certain physical peculiarities which render their immediate recognition not at all difficult. In general they are the offspring of an intellectual and nervously sensitive stock in which the evidence of other disturbances of metabolism—gout, asthma, and especially migraine—is not wanting. Quick, eager and vital, intensely aware of and interested in their surroundings, the children are prone to exhaust their meagre little bodies by the energy they throw into the whole business of life. There

is generally little doubt about their cleverness although their conspicuous lack of concentration and of dogged perseverence, their restlessness and their irritability may prevent success in school life.

The symptom of which complaint is most usually made is their liability to sudden " turns " or " attacks " or " bouts," as the mother may phrase it. They seem to have an inveterate tendency to fall suddenly and unexpectedly from a height of well being to a level which is very much lower. In the most typical cases these recurrent attacks culminate in, and the clinical picture is coloured by, the excessive emesis. But it is quite usual to find that only a few of the attacks have so culminated in vomiting, while often, although nausea is a pretty constant symptom there has never been any vomiting at all. Whether there is actual vomiting or not the complaints remain remarkably stereotyped. In almost the same words mother after mother will refer to such symptoms as great and rapid loss of weight ; pallor with puffiness and lividity under the eyes ; prostration ; muscular laxity and muscular pains ; abdominal tenderness and pain, intermittent and usually of short duration ; constant yawning or sighing ; constipation ; foul smelling breath ; excessive perspiration and breathlessness on exertion ; giddiness or faintness on rising in the morning ; a persistent irregularity of the temperature chart.

In a child of this inheritance, with a high but unstable metabolism, attacks such as those described above may be produced by three sets of causes.

(1) *By undue excitement.* Thus a child who had been to a theatre and had to be taken home, vomiting and collapsed, was found to have very extreme ketonuria.

(2) *By undue exertion.* It is a very usual complaint that these children are unable to travel by train or in a closed motor car. Ketonuria and a low blood sugar have been found in many cases of train sickness in childhood.

(3) *By infection.* It is this last factor of infection which has to be very carefully considered because of the confusion in the clinical picture which is thereby induced. In this particular child whom we are now considering an infection of whatever nature—a common cold for example which runs through a whole household, an attack of tonsilitis or of appendicitis or of pyelitis—will be as it were camouflaged. The well recognised and familiar symptoms of the " attack " are at once in evidence and may completely obscure, if we are not careful, the evidence of the underlying infection. There is considerable risk in such a child for example that an attack of appendicitis may for long pass unrecognised because the illness is presumed to be an uncomplicated attack of the well-known sickness. Close observation should prevent such mistakes. The new and uncontrollable factor of infection is apt to deflect and generally prolong the familiar outline of the attack. In practice, as might be expected, the recurrence of the attack is often determined by the existence of persistent sepsis in the nasopharynx. On the other hand in many cases it is very clear that a catarrhal reaction in the mucous membranes—especially stomatitis, mucous colitis, anal and vaginal irritation, curious white

scaly patches on the skin of the cheeks, cracking of the lips, heralds or accompanies an attack and is a result of the metabolic disturbance not a cause of it. It may be worth while to consider a little in detail from the clinical point of view of a few of the more important symptoms enumerated, such as amyotonia, vasomotor instability, abdominal pain, irregular pyrexia, and the cyclical character of the disturbance.

Amyotonia.

Postural defects, because of the striking tonelessness of the whole muscular system, are commonly found. The whole body droops and sags. Instead of being braced by strong muscular support, the body when upright is balanced in the position of least resistance. The normal postural curves of the spine are greatly exaggerated. To balance the weight over the stance, the shoulders are carried far backwards, and the resulting lordosis throws the abdomen into undue prominence. A secondary compensatory curve in the cervical region is necessary to bring the eyes into line. The weight of the dependent arms bring the shoulders forward and everts the vertebral borders of the scapulæ. The feet are apt to be flat, the knees a little hyperextended. The child tends to lean against any support which offers—his mother, a table, the wall. His power of making that sudden movement of recovery, which may be necessary to prevent a fall is very defective. A slight push may be all that is necessary to upset his balance. Prolonged standing or walking readily produces fatigue. The child is apt to make frequent complaints of transient pains in the muscles of leg, back or shoulders, a complaint which sometimes arouses groundless fears of subacute rheumatism. Postural albuminuria is very common.

Vasomotor Instability.

Together with this amyotonia of the muscles of abdomen, back and limbs, there invariably goes a certain weakness of the vasomotor tone. Thus complaint is almost always made of the pallor of the face and of the dark-rimmed eyes. During exertion or during excitement the face may flush readily, but in the reaction afterwards the pallor is often extreme. In children who have a fixed colour in the cheeks the change may show only around the mouth and eyes. The exercise tolerance is usually low, and breathlessness, with tumultuous action of the heart, is readily provoked by prolonged exertion. Extra systoles and functional heart murmurs are common. Syncopal attacks in older children are not rare. A diagnosis of dilatation of the heart is often made and prolonged rest in bed ordered, or because of aches and pains in the limbs, together with cardiac murmurs and cardiac irregularity, confusion arises with subacute rheumatism, with the same result that prolonged rest in bed is ordered. Yet I think that no type of child stands being bedridden so badly. Lack of tone in the skeletal and in the vasomotor muscles is increased by prolonged confinement to bed, so that the children when at length they are allowed to get up again, tend to show a veritable bed ataxia, with great inco-ordination in movement, giddiness and perhaps fainting.

Abdominal Pain.

Co-incidently with the attacks of pallor there is apt to be complaint of epigastric pain and discomfort. Such pains are as a rule transient, lasting perhaps but half-an-hour at most, and are often relieved by warmth, by lying down, or by any measure which improves the skin circulation. They are apt to be induced by fright as by a visit to the doctor, by exhaustion, and by the long day spent in the upright position. When seen during an attack of pain there is often considerable abdominal tenderness—sufficient apparently at times to lead the surgeon to remove the vermiform appendix.

Irregular Pyrexia.

Lastly, and this very greatly adds to the difficulty of diagnosis, it is characteristic of these children that the curve of the temperature, taken as is commonly done morning and evening, shows wide divergence from the normal. The so-called monothermia of health seems dependant upon the efficiency of the vasomotor tone. It is true that close inspection of the chart will often show that the subnormal readings are quite as frequent and quite as considerable as those above the normal. Nevertheless, the evening rise of temperature is a frequent cause of anxiety. The aspect of these thin and fragile-looking children whom nothing will fatten is apt to rouse the fear of tuberculosis in the minds of parents, which the evening rise of temperature seems to confirm, nor is it difficult to add further evidence in the shape of an X-ray examination of root shadows of the lung and a positive von Pirquet test. I admit the difficulty of arriving at a right decision in every case, but I feel that in general a diagnosis of tuberculosis must be based on more definite evidence than this. Sometimes indeed the level of the temperature curve is definitely raised for weeks or even months at a time. In such cases a fall to normal can often be achieved by cutting down considerably the intake of food. Dr. Eustace Smith indeed was accustomed to speak of this form of pyrexia as " Food Fever."

The Cyclical Character of the Disturbance.

Amyotonia with transient muscular pains, vasomotor pallor, and cardio-vascular weakness, with abdominal pain or discomfort, and irregular pyrexia, are perhaps the most common symptoms. Constipation is the rule ; headache and giddiness only occasional complaints. But through all there runs the story of the tendency to live, as it were, on a curve with sudden bouts of prostration and perhaps of vomiting. In many, indeed, the vomiting is by far the most prominent and most distressing symptom. Suddenly, or perhaps after a short prodromal period, marked it may be by pallor, prostration, much yawning and refusal of food, the vomiting begins. While the vomiting is at its height, acetone is generally detected in the breath and in the urine, but its presence in great amounts often follows and does not precede the vomiting. We still lack figures which show quantitatively the output of acetone bodies in children such as I have described during the mild or abortive attacks not culminating or only occasionally culminating in severe vomiting. Langstein and Meyer[8]

have shown that in children the greater part of the acetone bodies are excreted in the breath and not in the urine in which alone detection or estimation is clinically easy.

Whether the attacks are mild or severe, whether with or without actual vomiting, they tend to repeat themselves monotonously, with a strong resemblance one to the other. Sometimes they are preceded by a period of almost exaggerated well-being, when the eye is at its brightest, the energy and appetite of the child apparently greatest. Many mothers have remarked that they have come to dread overhearing their friends congratulate them on the apparent improvement in the child's health, because they have learnt that such congratulations usually herald one of the inexplicable " attacks."

Disturbances of Metabolism, Infection and Nervous Unrest.

That the child with an unstable nervous system has a relatively unstable metabolism may perhaps be taken for granted. That faults of management which produce restlessness, irritation and outbursts of temper, increase this instability of metabolism seems to me clear. Nevertheless, the reverse is also true and the metabolic disturbance is not without influence in producing the symptoms of nervous unrest. It is during the attack of prostration and pallor that the " contrary " child becomes most " contrary," that the timid becomes most timid, the miserable most miserable. At those times lessons usually easily mastered may become far beyond the child's powers. If it is true that the nervous unrest provokes the metabolic crisis, it is equally true that the metabolic crisis may provoke or perpetuate nervous unrest.

No doubt both ketonæmia and hypoglycæmia may be present in the great majority of children without any very visible disturbance of health, yet I think it may be said that, given a certain temperamental and metabolic inheritance, we may recognise a type of child in whom not only are ketonæmia and hypoglycæmia relatively easily produced, but the reaction to these disturbances is characteristic and of the nature described. In such cases it is always worth while to investigate the therapeutic results of an antiketogenic diet prescribed for some weeks, and to combine the relatively high intake of sugar with the daily administration of an alkaline aperatif. Especially when the element of chronic infection is absent improvement may be very striking. It must be remembered that the child depicted above—lax, pale and exhausted—is often a notable cold-catcher with a low immunity against catarrhal infections of all sorts. With improvement in colour, energy, muscle tone, and capacity for exercise, resistance against infection is increased. It is often a difficult task to separate the infective from the metabolic component in the child's illness, and to decide which has played the primary part and which the secondary. Infection is often a cause of the metabolic disturbance, sometimes a result.

To recognise in a child a condition of ketonæmia is not, of course, to achieve a complete diagnosis. The condition is but an extreme reaction in a particular

type of child to various stresses, and most frequently of all to underlying infection. The particular nature and site of the infection often remains to be determined.

Cyclical vomiting, even in its most fully developed form, is a disturbance by no means rarely encountered among the children of the well-to-do. If we include all these milder cases in which the symptoms stop short, as it were, at a lower stage of development and do not culminate in vomiting, the disturbance becomes of every-day occurrence. The study of a diathesis presents this difficulty—that the severe cases on which all would be agreed are separated from the normal by every possible gradation, and there is danger lest the enthusiast discovers its traces everywhere.

In treatment we have to consider at once the parts played by infection, by diet, and perhaps above all by management. When busy, happy and occupied, these difficult little people thrive and are often free from attacks. With unsuccessful management the negativism, the irritability, the restlessness, and the lack of emotional control, lead directly to exhaustion, and provoke the metabolic disturbance which culminates in the disastrous attack.

As with asthma, epilepsy, migraine and many other allied cyclical disturbances, one has the feeling that each attack predisposes to a recurrence, while a long period of immunity seems to increase resistance so that a relapse is only occasioned by a much greater stimulus.

If perhaps in this address I have occupied time with many matters that seem somewhat trifling and have passed a long way from those laboratory studies with which I began, I have the feeling that you will forgive me, because of all that we have learned from the teachings of Sir James Mackenzie, that which seems to me most true and most fundamental is the recognition of the importance for each one of us, in our little way, and in the measure of our opportunities, to busy ourselves in studying the trifling beginnings of ill-health.

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SOME INSPIRING CASES OF ACUTE RHEUMATISM

BY

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The difficulties in finding and clearing any path by which the various morbid conditions included under the general term of 'rheumatism' can be either linked up to one another or definitely separated, present a great problem in practical medicine. For this reason it must be a cardinal principle to endeavour to make some definite base from which further explorations can be undertaken and to which return can be made for a fresh start, should these ventures prove unsuccessful. This is the essential reason for establishing a definite disease, the acute rheumatism of childhood, and I am of opinion that in so far as any disease is an entity this acute rheumatism is definite. True it may shade off in many directions but the mean of numberless observations is a morbid condition with a well established pathological anatomy and clearly recognised cardinal symptoms.

The study of such a disease may be directed to the clear exposition of its classical features, its course, prognosis and treatment; or again may be directed to the more unusual cases from the standpoint of their bearing upon the wider problem of rheumatism. Such cases I term 'inspiring' because they lead our thoughts out of the ordinary groove, and though these thoughts may be of the nature of speculations and therefore always open to error, they are nevertheless, as it were, mental tonics. Some of these unusual cases are commented upon in this article and the lines of thought they suggest indicated. I am, then, dealing with some unusual examples of, or contingent to, acute rheumatism, which are not only of interest in themselves, but are valuable because they lead one to think of the variable behaviour of the rheumatic infection or infections, and may possibly give to some investigator who is carrying on the exploration of rheumatism in general some hint which may lead to further advances. There is no doubt one danger to be avoided in a study of this kind, and this is to allow the unusual case to upset our standard. For example, a case will be touched upon in which the prominent feature was the occurrence of many nodules without any grave disease. Dr. Cheadle long ago pointed out that the occurrence of nodules meant severe heart disease and not rarely a fatal illness. Statistics have entirely supported this view, and my own figures from various series have convinced me of its essential truth. This unusual case cannot then be used to controvert a general rule, but it can be used to stimulate interest in the occurrence and meaning of these nodules.

In another example the commencement of an attack of acute rheumatism with acute heart block as the first manifestation leads one to think of the rheumatic myocardial lesions, always a difficult yet most important aspect of rheumatic heart disease.

In a third case the occurrence of an enlargement of the thyroid gland coincident with a severe cardiac rheumatism reminds us that for many years acute rheumatism has been cited as an antecedent of exophthalmic goitre, and yet in a wide experience, it is only very occasionally that I have been able to trace a *direct* connection between acute rheumatism and an obvious disturbance of the thyroid, though I have with comparative frequency found a record of previous acute rheumatism in the history of exophthalmic goitre.

CASE 1. *Acute rheumatism starting with heart-block.* The first case was that of a boy, W. S., aged 13 years, a nervous but athletic lad who on January 17th, 1923, developed a sore throat, not of great severity but definite. Four days later he suddenly had pain in the chest, fainted and vomited, and these fainting attacks were repeated. A natural suspicion was diphtheria. There was, however, not the least evidence of this infection, but the condition was one of obvious heart block, the auricles beating at 72, the ventricles at 36. I considered the symptoms to be of the Stokes-Adams type, but the cause of the heart-block mysterious. The mystery was, however, soon cleared up, for shortly afterwards he developed chorea and acute multiple arthritis with endocarditis of the mitral and aortic valves. His condition became a very serious one and the illness extended over months but the heart block was transitory and lasted only a few days. A slight mitral systolic bruit with cardiac dilatation was detected after this phase of heart block had passed and the boy kept strictly in bed and it was then that the chorea and the acute arthritis showed the cause of the heart block. The chorea was an interesting one. It began quietly but eventually developed great severity and there were complete dumbness and urgent illness on account of the heart disease. He made eventually a good recovery but the heart was severely damaged by the endocarditis of the two valves.

This onset of acute rheumatism with heart block has been repeatedly observed, and we owe to Dr. G. A. Sutherland his experience of the value of adrenalin subcutaneously in 1-1,000 solution for dealing with the urgent symptoms. To me it is also an event of extreme interest, for so far back as 1899 I demonstrated at the then Royal Medico-chirurgical Society the scattered focal lesions produced by acute rheumatism in the myocardium. All know them now as Aschoff's nodules and as having a special structure. When the work of the late Sir J. Mackenzie, Sir T. Lewis and all that great band of investigators threw light upon arrhythmias, it was obvious to me that the scattered lesions of acute rheumatic carditis might some of them damage the conducting system. Clinical experience, as shown by these cases of heart block gives support to that pathological work of the last century, though perhaps I am surprised that the phenomenon of acute heart block is not more frequent in the carditis of childhood. Of more general importance is the history of this case as an illustration of my central theme, the difficulty of the study of rheumatism and the need for inspiration. This boy, save for the heart block and the definite sore throat, had no signs of acute rheumatism, yet he developed an attack of a prolonged and severe nature, leaving permanent cardiac damage. In these days, very rightly, great attention is being drawn to the prevention of the disease in the young, but it is obvious that if such a severe case as this can begin so mysteriously, we must be prepared to be very patient while a greater knowledge of the disease is being built up and expect many difficulties in diagnosis even in this one branch of the general study of rheumatism, the acute disease in childhood. When we think of rheumatism in general we

should indeed be short-sighted if we did not forsee how long and intricate the study of such a problem will be, and how far we must travel from terms such as 'Intestinal toxæmia,' 'radio-active waters,' disturbance of 'endocrine secretion' and so forth. I do not say these terms are valueless, far from it; but they are at present only indications for research.

CASE 2. *Multiple nodules with apparently normal heart* The second case was a female child, P. B., aged four years, who had complained for a month of pain in all the joints and screamed when they were touched. There was also a history of abdominal pains which had been complained of for about 12 months and which were most definite before meals. At times also a rash appeared coincident with an outbreak of the pain and when this rash was severe blisters formed. There had been no previous attack or history of rheumatism in the family. On admission on October 16th, 1925, though rather pale she did not seem ill, and her appetite was good. There was complaint of pain in the elbow joints but no swelling and numerous subcutaneous nodules were seen along the extensors of the metacarpo-phalangeal joints of the hands over the left fibula above the left external malleolus and also over the back of the head.

The appearance of the hands, owing to the nodules, superficially resembled that of an osteo-arthritis in an elderly person. There was slight creaking on movements of the knee joints. For the pain in the abdomen no explanation was forthcoming unless it was neuro-muscular. *Her heart was normal* as judged by repeated clinical examinations. There was no chorea. The throat appeared to be healthy and there was no history of tonsillar trouble.

In brief, here was a child whose striking clinical signs were subcutaneous nodules of the classical type, and yet the heart was not affected and the child not apparently seriously ill.

We kept her in the hospital for over four months to make a careful study of her case and effect of the treatment. Throughout all these weeks her temperature was normal but crop after crop of nodules appeared on hands, elbows, knees, ankles and occiput; from time to time, also, a multiform erythema developed. chiefly on the abdomen, and the abdominal creases showed a peculiar redness. One nodule was removed for investigation, but the culture after four days was sterile.

The heart was occasionally quickened to 100 per minute, but averaged about 80. A sinus arrhythmia was frequently detected, but never a murmur.

General treatment was tried with salicylates, tolysin, and lastly anti-rheumatic vaccine; also radiant heat and massage and, later, artificial sunlight were employed.

She left the hospital on March 12th, 1926, by request, better than when she came in but not really free from rheumatism.

If we take the nodules as the index for the result of the treatment, in my opinion, not one of the remedies influenced the case.

Five days after leaving hospital she was brought back with slight but definite chorea, and it may be added here that her parents were both highly nervous people. Her heart was now quickened and the pulse 120 per minute and there was some dilatation, the impulse being one inch outside the left vertical nipple line. The first sound was short; there was sinus arrhythmia but no murmur or thrill. Once again there was a multiform erythema over the abdomen and an entire absence of fever. The chorea was at first slight and rapidly subsided and the heart became regular; but more nodules commenced to appear and a commencing mitral stenosis was suspected on account of an abrupt first sound. Next, the chorea now commenced to imitate the behaviour of the nodules by recurring and this time the child became quite dumb and the limbs showed the extreme paralytic type of the affection. The mentality also became very dull and the child looked seriously ill. There was a slight rise in the temperature for two days and then it returned to the normal once more.

It is very remarkable that in three cases in this article there was dumbness with the chorea. Well known as this symptom is, in my experience it is uncommon. Inability to speak on account of inco-ordination of the tongue

and lips is frequent enough, but this absolute speechlessness with no effort to attempt articulation is exceptional and a most striking clinical feature. This condition may last for weeks, but I believe myself correct in saying recovery is always complete. All these three children were excitable and intelligent even for rheumatic children, and each one it will be noticed had a very unusual form of acute rheumatism.

It may be asked, why call a case with no fever 'acute rheumatism' and the answer is that the most terrible cases of pericarditis in children are those which run a course with no fever. After the Great War two such cases were under my care, reacting to no remedies and dying in a few weeks without the slightest reaction. No illness could have been more striking in its deadly virulence.

I have seen this child recently: she is much improved and has no cardiac lesion, and the nodules have also disappeared.

The occurrence of subcutaneous nodules as the prominent feature in an attack of acute rheumatism is a fact that has been known for a long time, but such cases are most unusual, and on no account should they be allowed to alter the general rule that it is the severe cardiac cases in which these lesions are usually found. Every one who collects a series of cases of acute rheumatic carditis and analyses it, will find among the fatal ones a high incidence of subcutaneous nodules. For my own part, I have long been hammering at a closed door in trying to understand what is the real meaning of these nodules. It would appear now that the type of lesion is a response to streptococcal infection and I look upon them as local infections and am aware from an investigation I made with my colleague Dr. G. F. Still, that changes occur in the subcutaneous tissues in proximity to nodules which are identical but differ in that they do not form nodular projections because they are not over prominences. Dr. V. Coates has recently directed our attention to a miliary type of these nodules and once more roused our interest in them. Does, for example, the subcutaneous infection arise from the cardiac valves; I do not mean from gross emboli but from scattering of the infective agent? These observations seem to throw a little light upon the problem. Dr. Paine and I found and grew the diplococcus from them and actually saw it in a dilated capillary of one of them, and others have succeeded in demonstrating them. Why do they vary in frequency in different years? Again, what influence has movement and pressure upon their formation?

Undoubtedly we can see there is more to be learned about acute rheumatism before we can thoroughly interpret its various clinical features. In the *Archives of Disease in Childhood*, August, 1926 (pp. 183-193) a valuable paper was published upon the subject of rheumatic nodules by Vincent Coates and Carey Coombs.

CASE 3. *Severe rheumatism with thrombosis of inf. vena cava.* The patient, a boy, F. W., aged 13 years, was admitted to University College Hospital, on October 10th, 1922. Six months before this he had been noticed to have had twitching movements of the face and hands for about a fortnight. Three weeks before admission, he had an attack of acute rheumatic arthritis affecting the knees, elbows and hands, which subsided in a week, but was followed by chorea

which was at first mild but of the paralytic type. On admission, he was dumb and there was cardiac dilatation with mitral endocarditis. Four days later there was arthritis of the left elbow. The chorea was very unusual in type, with incontinence of urine, refusal to obey any simple commands and a mental state bordering closely on dementia varied, at intervals, by emotional outbursts. Later there were stertorous breathing and nystagmus and the pupils were widely dilated. The cerebrospinal fluid was sterile on culture. I would add here that in the last 18 months I have seen two cases of chorea with hyperpyrexia. Both of them recovered. To return: on October 26, the right leg commenced to swell from ankle to thigh. This swelling, which was an œdema, increased and the veins of the abdomen below the umbilicus became enlarged. On November 6 the left ankle became œdematous and the clinical picture of a thrombosis at the lower end of the inferior vena cava developed. During this period of urgent illness there were also pleurisy, grave suspicion of acute pericarditis, considerable but not unusual fever and multiple arthritis. Eventually he made a good recovery and proved to be a most intelligent boy. A slight degree of mitral stenosis was present and though the œdema of the legs mostly disappeared in bed it returned in the erect position. He was taken in again later for observation. His condition then resembled precisely one which is sometimes seen with thrombosis of the inferior vena cava after typhoid fever. Large veins were visible over the abdomen below the umbilicus in which the blood stream coursed upward. There was slight œdema of the legs when at rest and considerable œdema after standing and walking. The right leg was more swollen than the left. The general condition was otherwise good. All later efforts to trace this case have failed.

In 1898 I described three cases of extensive various thrombosis in acute rheumatism all affecting the upper extremities; in one child the superior vena cava and all its main tributaries were full of clot. For years I did not meet with another case, but some four years ago I saw three more all implicating the upper extremities and all associated with severe and active heart disease. This is the only case in which I have seen the lower extremities affected. In my early cases I attempted to discover in a fatal case whether it was a primary phlebitis, and to this view I inclined, or a primary thrombosis, but none of the other cases I have seen since was fatal. The other interesting point in this case was the intense mental change. On the whole, great mental degradation is rare in chorea, but cases in childhood occur, as I have seen, in which hallucinations have been prominent and the chorea otherwise not severe. In the acute rheumatism of adults there may be acute insanity without chorea, though this must not be mistaken for the delirium from salicylate poisoning or that which is sometimes met with in an attack of acute pericarditis. The two acute cases of insanity under my personal observations both made good recoveries.

Case 4. *Urticaria and painful joints.* The next unusual case, which I cannot claim as an acute rheumatism, was a boy, W. S., aged 8½ years, admitted to hospital December 19, 1925, for swelling of the joints and a rash, and sent in by my colleague, Dr. D. Paterson, as probably a case of Still's disease. In September he was hop-picking in Kent, when the rash suddenly appeared over the face, trunk and limbs and a few days later swelling of the joints of the fingers and toes occurred. Since that date there had been repeated recurrences, and the wrists, elbows, neck and shoulders had been implicated. The rash caused much irritation when it appeared and sometimes accompanied and sometimes followed rapidly upon the arthritic swellings. His mother attributed the illness to eating a "toad-stool," but there had never been any vomiting or diarrhœa or nervous symptoms such as we associate with such poison. The family and personal history threw no light on the condition.

On admission he looked tired and ailing, but except for a pale pink macular rash upon the thighs, buttocks, forehead and at the roots of the hair, there were no clinical signs.

A week after admission the temperature, previously normal, rose to 101° F., and continued as an intermittent pyrexia for ten days and then, after twenty four hours quiescence,ran for weeks an irregular course, occasionally reaching up to 102° or 103° F., but usually ranging between 100° F. and normal. His general condition was one of fatigue. Three days before the first rise of temperature, there was pain in the left ankle ; two days later this swelled and then the finger joints swelled and were painful and an erythematous rash appeared over the trunk, urticarial in type. There was no enlargement of the spleen or lymphatic glands.

Dr. H. F. Turney, my house physician, investigated the protein reactions and found a definite and general sensitisation to all the proteins. Blood culture was negative. Culture from the urine was negative. Bacterial examination of the fæces showed no abnormality. Dr. A. H. M. Gray also kindly examined the case for me and confirmed the essentially urticarial character of the eruption, suggesting the presence of some local focus of infection. His tonsils were apparently normal and had never given trouble, but three unhealthy teeth were extracted. Every search for a definite focus was negative. Aspirin relieved the arthritic pains, and on account of the hypersensibility to protein, a course of intravenous peptone injections was given by Dr. Turney. Armour's No. 2 5% peptone was used and two minims of this were made up to ten with normal saline. The injections were given twice a week and the protein increased each time by 3 minims. Salicylates and Tolysin were also tried and careful dieting, but none of us felt that any of our treatment had influenced this mysterious illness which continued to show the same recrudescences, and supported Dr. Paterson's view that it was a case of the Still type, in spite of the absence of an enlarged spleen and lymphatic glands. Eventually he gradually recovered, yet quite recently he had some pain in his ankles.

This case, whatever may be its exact nature, appears to me of such interest from the fact that a definite sensitisation to protein was demonstrated. It throws, as it were, a glimmer of light on the metabolic problem in disorders of this type. We all recognise the striking example of metabolic disorder with arthritis in the well known disease gout, and the very existence of such a condition must always be a perpetual reminder of the possibility of some subtle change in metabolism in such conditions as acute rheumatism and rheumatoid arthritis and this is supported in acute rheumatism by the well known hereditary factor. In acute rheumatism there seems little doubt that the element of infection does in many cases in childhood dominate the illness, but the problems still remain as to whether, on the one hand, the predominance of the infection is not in part the result of some latent metabolic weakness, and on the other, whether in the prolonged and recurrent type of the disease the infection itself does not gradually produce such a weakness.

Case 5. *Malignant endocarditis supervening on rheumatic carditis.* This boy, C. H., whom I watched carefully for ten years, interested me very much, for in 1915 he was under my care in hospital with acute rheumatism and severe endocarditis damaging the mitral and aortic valves. It is these cases where both valves are affected in which I suspect a malignant tendency, for the fact of the multiple lesions occurring in the two valves so closely situated to one another suggests in itself this type, although at first both these lesions may scar and quiet down.

In 1917 he had another attack of acute rheumatism and in 1918 a severe pericarditis with prolonged fever and extreme dilatation of the heart. His life hung long in the balance, but after many months in hospital he made a good recovery and came to report to me every six months or at any time he had warnings of rheumatism.

He was a very steady boy with good parents and became a clerk. Year after year he reported to me and grew to be a well developed young man in spite of his much damaged heart which showed free aortic regurgitation and mitral stenosis. All these years his health remained remarkably good and he kept at work, taking good care of himself.

In May, 1925, he began to feel generally ill and came to hospital, but by a sad chance I did not visit that day and he unfortunately returned home without seeing me, intending to come the next week. In the meantime he developed what was called "influenza" and took to his bed with much pain over the heart and great illness.

He was finally admitted on June 5 extremely ill with high fever. An important point in his case was the condition of his teeth, which were unhealthy. One had been removed some weeks before and the gums had been septic. In the hospital cultures from the blood gave a pure growth of a non-hæmolytic *streptococcus viridans*.

It is not necessary to dwell upon the details of a very distressing and acute malignant endocarditis with cerebral and arterial embolisms and rigors ending in death, but a few details of the necropsy are of value.

There were exuberant vegetations on the mitral and aortic valves, numerous infarcts in the spleen, both recent and old; an embolus in the right common iliac artery with another in the left popliteal artery and a large embolus with consequent softening of the right parietal lobe. In spite of the high fever and repeated rigors there was no suppuration.

This case in turn opens up the well-known and most important question of progressive or malignant endocarditis which has rightly attracted great attention in the world of medicine. I need not dwell upon my own views on this question which have been so often expressed in various papers, but put forward some definite questions for consideration. The first is this. Is it advisable to make a time definition in these forms of endocarditis? By this I mean, is it advisable to think of a disease in the terms of acute, subacute and chronic infective endocarditis? May not these be phases of any infective endocarditis? Secondly, does not such a terminology suggest a non-infective endocarditis, and are we prepared to admit such a condition? Thirdly, though rheumatic endocarditis generally heals as do the nodules, the chorea and arthritis, are we prepared to say it always heals, and if it does not, what kind of illness do we think will result?

Attempts to answer these questions at once lead us into the midst of some of the greatest problems in the general study of rheumatism.

Case 6. *Chorea and enlargement of thyroid.* The last case was that of a girl aged 16 who at the age of 11 years had a short attack of chorea and in September, 1924, scarlet fever followed by rheumatism. In 1925 she was operated upon for enucleation of the tonsils and removal of adenoids, after which she had no more rheumatic pains, but during this last year, except for an interval in the summer, suffered from a moderate and stubborn chorea. This girl on admission to hospital, November 28, 1925, had definite chorea and aortic endocarditis, but the most interesting feature was an enlargement of the thyroid gland moderate in degree but very definite. It was firm in consistence and the right lobe was rather larger than the left. Arterial pulsation could be detected and there was fine tremor of the fingers, but no exophthalmos, and the pulse rate which ranged around 80 to 90 per minute was no swifter than would be expected from the organic heart disease. This thyroid swelling had been noted for some years but could not be accurately dated and varied in degree, and increased with exacerbation of the chorea.

In hospital she did well and the thyroid diminished in size. Further observation and treatment by Lugol's solution of iodine confirmed the general improvement and the consistence of the thyroid became firmer and the fine tremor diminished. She is still under observation.

Once again this case opens up a field for thought and observation and Dr. L. J. Llewellyn has in particular laid stress upon disorder of the thyroid in rheumatism.

By a coincidence while engaged upon this article another case of acute articular and cardiac rheumatism in a female patient followed *at once* by enlargement of the thyroid and the definite signs of Graves's disease came under observation. In her case there had been the factor of great nervous strain preceding the attack of acute rheumatism.

At the present time also I have under my care a third case, a child aged 13 years, a girl of very excitable temperament, who had been under my observation in hospital for chorea in 1923, and again with a very severe attack in 1925. On the second occasion her eyes appeared to be more prominent but there was no enlargement of the thyroid gland. For the third time she was admitted on December 18th, 1926, for a recurrence of chorea of a fortnight's duration. She now showed an enlargement of the thyroid affecting both lobes, obvious exophthalmos, Stellwag's sign, fine tremor, and a rapid heart with an occasional systolic murmur in the mitral area. It would appear that in 1925 there was some hyperthyroidism as shown by the commencing exophthalmos, but that the thyroid was not enlarged or, to be more cautious, not sufficiently enlarged to attract attention. During the interval between 1925 and 1926 the child was apparently well and her mother had not noticed any swelling of the neck, but when admitted to hospital with the renewed chorea, the enlargement was very apparent and there were also other clear signs of exophthalmic goitre.

It is no new idea that the thyroid is affected in acute rheumatism, but when one looks back upon the many cases of the disease one has seen, the firm impression is left that if the thyroid is often affected the gland itself rarely shows any gross evidence of disease. In some cases of chorea I have noticed enlargement of the thyroid, but in hundreds I have seen no change. Yet we must allow that there may be a subtle alteration in the secretion without any clinical evidence, and possibly prolonged studies of the basal metabolism may prove a source of further light. Acute rheumatism is a disease in which we might well expect some thyroid change, when we recall the peculiar nervousness of the rheumatic and also those cases of irritable heart in the rheumatic in which we are doubtful whether the condition is due to some neuro-muscular damage to that organ, or to some circulating poison or disordered metabolism which is disturbing a heart but producing no definite myocardial lesion. The same possibilities, it will be remembered, have also arisen over rheumatoid arthritis. No thoughtful observer who accepts acute rheumatism as infective in origin can doubt that in this disease there is also probably some peculiar metabolism, whether innate or produced by the poisons linking themselves into the very tissue cells of the patient. This is an aspect of rheumatism which has always attracted me because of the inveterate course of many cases and the different behaviour of the lesions at different ages.

It may be thought that I have wandered far afield into speculation, but this is the result of inspiring cases. Such do not allow us to be content with bare enumeration of symptoms and signs. There are occasions when it is advisable to keep on the beaten track and drive home the essential features

of classical cases, but equally there are occasions when it is useful to imagine what great fields there are before future investigators. It is sometimes said that all the easy things in medicine have been already done, but these easy things were not easy when they were still problems, and future investigators have, among other encouragements, the rapidly developing science of bio-chemistry. Looking forward one can see that some day that great gulf will be slowly bridged which will enable the physician to link together the bacterial poisons on the one hand and the metabolic disorders produced by them in the human tissues on the other. This is one of the great difficulties in the study of rheumatism. No one is a firmer supporter of the belief of infection as a factor than I am, and I venture to think no one is less convinced that mere infection is the sole explanation of these diseases. But at the moment we are working in an atmosphere of mist because we do not know sufficient of the bio-chemistry of these diseases to recognise the bacterial and human sides in the many divergencies from the normal which are presented.

BRONCHIECTASIS IN CHILDHOOD.
Its Symptomatology, Course and Cause.

BY

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Introduction.

There are three conditions, viz :—bronchiectasis, chronic or unresolved pneumonia, and pulmonary tuberculosis, which have always given, and still do give rise to difficulty in their differentiation. Until recently the finding of the tubercle bacillus has been our chief, if not our only aid, in this differentiation, though from a knowledge that such is not always positive many cases of bronchiectasis and simple chronic pneumonia, at least in childhood, have been certified as cases of pulmonary tuberculosis and admitted to Sanatoria. It might be thought that with the advent of radiology great assistance would have been rendered in this direction, but when we recall that any consolidation of lung tissue will obstruct the passage of the X-rays and cast a shadow the limitations of this method of examination will be apparent. Nevertheless, if one appreciates the usual course of pulmonary tuberculosis during childhood, X-ray examination of the chest does give considerable help.

Pulmonary tuberculosis as it is met with by the pædiatrician is on the whole a disease of infancy and very early childhood, an acute or subacute ailment leading comparatively quickly to a fatal result, and, unless in the very early stages, involving both lungs. Chronic pneumonia and bronchiectasis, on the other hand, are met with as a rule during later childhood, are eminently diseases of long duration and usually, though not invariably, limited to one lung or one lobe of a lung. Hence the extent of the mischief in relation to its duration and the age of the patient may enable one to speak fairly definitely for or against tuberculosis.

Within recent years, however, Sicard and Forestier[1] have shown that it is feasible to introduce into the bronchial tree a substance (iodized oil—lipiodol) which is impervious to the X-rays. By this procedure it is possible to demonstrate the conformation of the whole bronchial tree and to discover if the bronchi, as in health, gradually taper towards their distal extremities or whether bulbous or tubular dilatations are present along their course. It is on the basis of our experience with this method of investigation of cases of chronic pulmonary disease in childhood, and the results obtained, that the present communication is founded. In our discussion of the question we wish to limit our attention to the matter of diagnosis and cause of the malady, and to the condition as met with during childhood. In view of the fact that many authorities are agreed that the onset of the disease, or at least the chronic pneumonia which is one of its main causes, is most frequent during childhood this limitation of the field of study does not produce such a one-sided view of the subject as might at first sight appear. In perhaps the largest series of cases of chronic pneumonia and bronchiectasis, which was recorded by Clark, Hadley and Chaplin[1a], 82% of 45 cases had their origin before 8 years of age.

Diagnosis.

Physicians have been familiar with the condition of bronchiectasis ever since Laennec first described it in his classical work entitled "De l'auscultation" published in 1819[2]. Laennec gives an almost perfect description of the symptoms and naked eye appearances and he records in detail two well-marked examples. These two cases occurred at the two extremes of life and illustrate some of the most characteristic features of the disease. One case was that of a child of three years who contracted whooping cough and in whom the cough persisted for six to twelve months, the child dying during one of the paroxysms of coughing. The other was a maiden lady of 72 years who had suffered for at least 50 years from a malady of the chest characterized by cough and purulent spit and frequent hæmoptysis. Though these symptoms suggested pulmonary tuberculosis she was quite able to attend to her labours as a teacher of the pianoforte, was well formed and did not emaciate. Death ensued comparatively rapidly at the end with severe dyspnœa and œdema. In the child, fibrosis of the left lower lobe and bronchiectasis were found at the post-mortem examination. In the adult, fibrosis and numerous cavities with smooth walls communicating with the bronchi were found in the right upper lobe : in the right lower lobe there was also some slight dilatation of the bronchi, as also in the left upper lobe, but in neither of these lobes were there any definite cavities : the left lower lobe was quite free and the heart appeared healthy.

Laennec gave as the characteristic clinical picture a disease of long duration accompanied by severe fits of coughing, abundant muco-purulent spit and pectoriloquy audible at some part of the chest, but unattended by fever or emaciation. Curiously he makes no mention of amphoric breathing to which nowadays so much attention is paid and which is often a most characteristic feature, especially when searched for after emptying the bronchiectatic cavities by inverting the patient and getting him to cough—the so-called posturing. The first writer apparently to draw attention to amphoric breathing was Andral[3] who, when describing a case in 1824, says that "a species of bronchial respiration occurred as if the individual was blowing strongly at the extremity of the cylinder."

When the symptoms and signs are present in their classical form the diagnosis is easy, but most authors admit that a complete picture seldom obtains and hence the frequent difficulty in diagnosis. In fact during the last 100 years little change is to be observed in the attitude of different writers when discussing the question of differential diagnosis, so that Laennec writing in 1819 is as modern as Fowler [4] writing in 1898 or Ewart[5] in 1909. This simply depends on the fact that dilatation of the bronchi does not always produce signs or symptoms and that there has been no method by which during life a bronchial dilatation could be definitely demonstrated. Armand Delille[6] who has perhaps within recent years written most extensively on the question, at least in childhood, groups the cases under two headings : (*a*) those with typical symptoms—cough, spit, pulmonary dullness and amphoric breathing, and (*b*)

those with typical symptoms having the manifestations of bronchitis or recurrent colds or perhaps no symptoms at all, as when the condition is suggested from the appearances accidentally discovered during a radiological examination of the chest. In Delille's opinion the majority of cases in childhood belong to the second group. Delille also draws attention to the fact that physical signs of bronchiectasis may be present while lipiodol injection may reveal a normal calibre of the bronchi.

Like most clinicians we not infrequently had met with the greatest difficulty in arriving at a definite diagnosis. From the collation of our clinical and post-mortem material we had become fairly confident in the recognition of tuberculous lesions, even although tubercle bacilli could not be isolated from the sputum. As previously mentioned the age of the patient, the rapid course of the disease and the fact that X-ray examination usually revealed mischief in both lungs, and much more extensively than was evident by physical examination, were all points which helped us to separate the tuberculous examples from other chronic pulmonary lesions. And from the not infrequent and unexpected finding on the post-mortem table of bronchiectasis in cases which had been diagnosed as chronic pneumonia we were coming to believe that these two conditions were always co-existent, and that chronic pneumonia and bronchiectasis might be used as synonomous terms. It was consequently with the greatest interest that we availed ourselves of the help of the intratracheal injection of lipiodol to test our views on this question. As the result of this experience we have modified our opinion that chronic pneumonia is invariably accompanied by bronchiectasis, although we still hold that such is usually the case. We have also learned to appreciate with Delille that in not a few instances the latter condition may be present though there are no signs of its existence, and further, that both signs and symptoms may definitely point to its presence when there is absolutely no dilatation. From our premature confidence in the reliability of physical signs we at first were inclined to the view that the use of lipiodol would be chiefly of academic interest and not necessary for formulating a diagnosis, but we now feel that this method of examination is really essential, not only for arriving at a diagnosis, unless in those cases where the classical symptoms are present in their most typical form, but also to demonstrate the full extent of the disease.

Before reviewing our conclusions regarding the signs and symptoms and clinical course of the disease from an analysis of all the material which has come under our notice we have considered it advisable to give in the first place detailed histories of several contrasting cases. In this way our point of view will be best exemplified and the help given in diagnosis by the intratracheal injection of lipiodol demonstrated.

Case 1. The first case was a boy who came under observation in 1914 at the age of 4½ years with a history of cough and fever and loss of flesh of one month's duration. On admission to hospital the left side of the chest, both back and front, was dull to percussion, with the R.M. tubular towards the apex and very deficient towards the base. X-ray examination revealed

mottling throughout the whole of the left lung. Irregular intermittent fever persisted throughout his residence of three months in hospital, but with little change in the physical signs. On several occasions owing to the density of the dullness and marked deficiency of the R.M. fluid was suspected and the chest was explored but always with negative result. Sputum was also obtained on several occasions but tubercle bacilli were never found. The diagnosis wavered between chronic pneumonia, empyema and pulmonary tuberculosis and when he died suddenly one morning, 4 months after the onset of the illness, from a most severe hæmoptysis, tuberculosis was thought to be the most probable lesion. At the post-mortem examination the left lung was found shrunken and adherent all over with the surface like that of a cirrhotic liver. On section the interlobular fibrous tissue was seen to be greatly increased in amount and enclosing cavities with caseous looking walls which histological examination revealed to be dilated bronchi. The hæmorrhage had apparently arisen from one of the larger cavities at the extreme base of the lung. The right lung was very emphysematous. No evidence of tuberculosis was discovered anywhere.

This case occurred before the use of lipiodol had been advocated and before we had formulated our ideas regarding the clinical features of chronic pneumonia and the frequency of pulmonary tuberculosis at this age period. The picture, however, was typical of unresolved or chronic pneumonia, and, with the exception of the persistent cough, there was no sign or symptom usually considered characteristic of bronchiectasis. It was this case and several almost exactly alike in symptomatology which had led us to consider bronchiectasis and chronic pneumonia as one and the same pathological entity.

The following case (Case 2) is one with a somewhat similar history to that above detailed, but differs in that we were ultimately able to avail ourselves of the help of lipiodol injection.

Case 2. An illegitimate boy *aet.* 8 months was admitted to hospital with a history that six weeks previously cough, fever and dyspnœa had developed and that on being seen by a doctor pneumonia had been diagnosed. He seemed to improve after a little but one week ago cough and dyspnœa returned. On admission to hospital there was no fever but the breathing was rapid and grunting in character; there was dullness to percussion all over the left side of the chest with an intensely tubular R.M. all over the left back and in the left lateral region. X-ray examination showed a shadow throughout the left side of the chest with the heart pulled to the left and a suggestion of cavitation or clearing at the apex.

The further course of the illness was characterized by an almost complete absence of fever, persistence of physical signs of consolidation of the left lung and possible cavitation at the apex suggested by the occasional amphoric nature of the breathing and the X-ray picture. Tubercle bacilli were not found in the sputum examined on several occasions. Though the physical signs did not suggest fluid its presence was regarded as not improbable by the radiologist and the chest was explored but with negative result. The case was looked upon as one of chronic broncho-pneumonia and treated with a mixed influenza bacillus vaccine without any apparent benefit. He remained in hospital for two months and was then sent to a convalescent home where he remained for a further period of four months. During this time he had comparatively little cough and no fever. He steadily increased in weight, but the physical signs remained unchanged except that the apex seemed clearer to percussion and on examination with the X-rays. He was re-admitted to hospital eleven months later when aged 2 years for further investigation. The mother stated that cough was still present being specially severe in the morning when it might continue for as long as an hour at a time. There was no spit. Only once during the interval had he had any manifestations of acute illness when he suffered from fever with dyspnœa and respiratory dilatation of the nostrils for one day. The child had grown and learned to walk and run about and play. On re-admission he looked a fairly healthy boy and his height was only 2 cms. below Holt's average. The left side of the chest was slightly flattened and dull to percussion, both back and front, with definitely amphoric R.M. at the angle of the scapula.

10 cc. of lipiodol were injected into the trachea through the crico-thyroid membrane and an X-ray photograph taken immediately afterwards revealed dilatation of the bronchi throughout the whole of the left lung. (*See* Fig. 1).

In the next case (Case 3) the history, signs and symptoms were classical and the lipiodol injection fully confirmed what was anticipated.

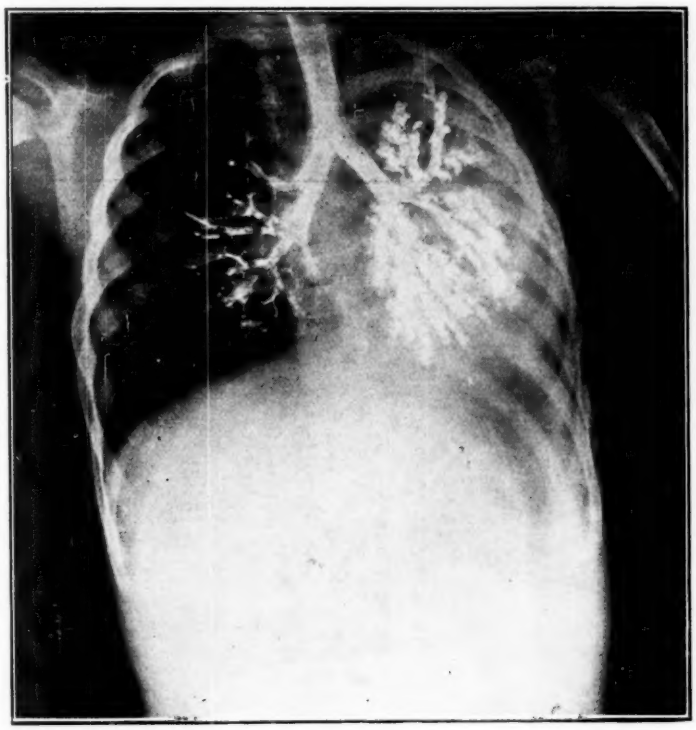

Fig. 1.—Case 2. Extreme degree of tubular bronchiectasis throughout whole of left lung.

Case 3. A. McM., a girl, came under observation on October 2nd, 1924, at the age of 7 years on account of a persistent cough and profuse yellow spit. She had had pneumonia after measles when twenty-one months old and since then cough and spit had been present, and although varying in severity had on the whole got worse. At times blood was present in the sputum. She had been resident for six months in a sanatorium at the age of 5 years because she was supposed to have pulmonary tuberculosis.

She was an undersized child with a height of 106.5 cms. and a weight of 13.4 kilos. Her colour was good but fingers and toes were clubbed. Von Pirquet's tuberculin reaction was negative. The cough was very troublesome and came on after the least exertion, and the sputum, which seemed to be brought up in mouthfuls, varied in a day between 2 and 5 ozs. The sputum consisted of liquid greenish pus and was devoid of all odour. The left side of the chest was flattened and dull to percussion in the lateral region and over the back below the angle of the scapula : the gastric crescent was on a level with the 5th rib and the heart was drawn over to the left with the apex beat in the 5th space 4½ ins. to the left of mid-sternum. The R.M. was tubular at the apex and deficient at the base. After " posturing " and evacuation of about ½ oz. of liquid pus the dullness at the left base was less intense, the R.M. became amphoric and whispered

pectoriloquy was audible in the region of the angle of the scapula. X-ray examination of the chest showed a distinctly "honeycomb" shadow in the lower half of the left chest and after lipiodol an extreme degree of saccular dilatation of the bronchi in the left lower lobe. (Fig. 2).

The following case (Case 4) is one in which the symptoms were as equally characteristic as in the preceding case, but the physical signs were not commensurate with the extent of the mischief.

Case 4. R.R., female aged 13 years, came under observation, Sept. 6th, 1926, with the complaint of cough since the age of one year. She had bronchitis at one year of age, broncho-

Fig. 2.—Case 3. Saccular bronchiectasis in left lower lobe.

pneumonia at twenty months and again at two and a half years, since when the cough and spit had been specially troublesome. The cough was most frequent in the morning and was accompanied by a profuse yellow spit. She was a healthy looking girl only very slightly under height and weight, measuring 152 cms. and weighing 37 kilos. She had a good colour and there was no clubbing of the fingers. The cough was very troublesome and was induced by the slightest movement when she would expectorate a large amount of a yellow but odourless sputum. The von Pirquet tuberculin reaction was negative. Physical examination of the chest revealed defective movement of the left side with some harsh and dry râle and a tubular R.M. just below the angle of the scapula. There was little or no change in the signs after posturing and expectoration of some muco-pus. X-ray examination of the chest showed little else than increased root

shadows. After injection of lipiodol, however, an X-ray photograph revealed marked dilatation of the bronchi in both lower lobes, but more extensive on the left side. (Fig. 3).

The next case (Case 5) is one in which both signs and symptoms were indefinite but lipiodol revealed very definite bronchiectasis.

Case 5. A.T., a female, aged three years and ten months, came under observation Oct. 7th, 1925, with the complaint that for two years she had had a cough which during the last nine months had been accompanied by a yellow spit. She had measles at one year and pneumonia at two and a half. The cough had been present since the attack of measles and the spit since the attack of pneumonia. During the night, but especially on waking in the morning, the child was subject to fits of coughing when she brought up about one drachm of a yellowish spit. Otherwise she appeared perfectly well. She was a healthy looking child of normal height (97 cms.) but

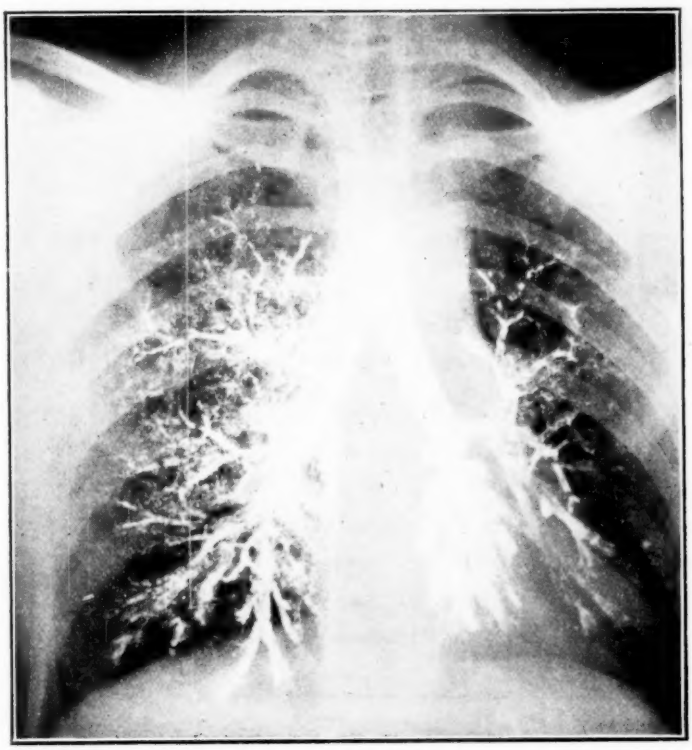

Fig. 3.—Case 4. Tubular bronchiectasis in both lower lobes.

slightly under weight (13 kilos). The von Pirquet tuberculin reaction was positive. Examination of the chest revealed an impaired percussion note over the right front below the nipple and in the left lateral region. The R.M. was tubular at the angle of the left scapula and was accompanied by much moist râle. After inversion and coughing, one half drachm of a greenish spit was obtained without change in the physical signs. X-ray examination of the chest revealed a doubtful fibrosis at the left base. Lipiodol demonstrated that the bronchi in both lower lobes, but especially in the left, were definitely dilated.

The next illustrative case (Case 5a) is one in which the history, signs and symptoms were as suspicious as in the preceding and from our previous experience of chronic pneumonia, we were prepared for bronchiectasis. Yet lipiodol did not reveal bronchial dilatation.

CASE 5A. M. McL., girl aged six years, admitted with a history of a cough which had been present since whooping cough two years previously. The cough was mainly during the night and on waking in the morning when she would frequently bring up yellow sputum. Six months ago the tonsils were removed without benefit to the child's general condition.

She was small, but well nourished; healthy looking; measured 106 cms. and weighed 14.3 kilos. There was dullness at the left base behind with high pitched and tubular R.M., almost amphoric at the angle of the scapula. Whispered pectoriloquy was well marked at the left base. The X-ray picture revealed a slight shadow at the left base. After the injection of lipiodol no dilatation of the bronchi could be made out and it was seen that the lipiodol had entered many of the alveoli giving a finely powdered appearance. (Fig. 4). (Compare with Fig. 5, which was also obtained in a case simulating in history and physical signs bronchiectasis.)

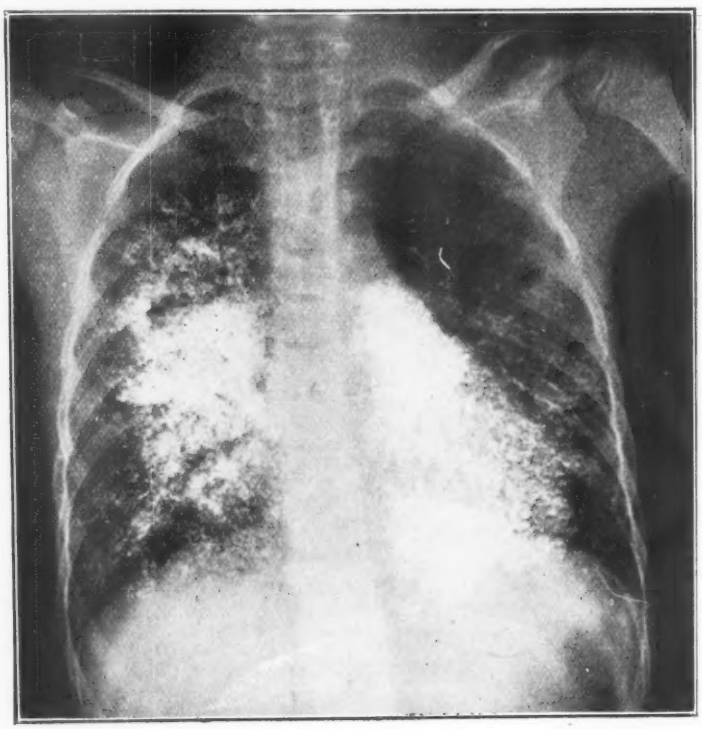

Fig. 4.—Case 5a. Appearance of lipiodol in alveoli. No bronchiectasis.

Finally the subsequent case (Case 6) is one in which there were neither symptoms nor signs of the condition and yet post-mortem examination revealed extensive dilatation of the bronchi in both lower lobes.

CASE 6. The patient was a girl (I. H.) who came under observation on August 8th, 1924, at the age of six and a half years with double pleural effusion, first on the left side and later on the right, and a positive von Pirquet reaction. From this illness she gradually recovered and remained in good health for some months. On February 16th, 1925, she complained of pain in the eyes but continued to go about as usual. On February 18th she developed severe occipital headache, became fevered in the evening (the temperature registering 103° F.) and was very restless during the night. Next day she vomited frequently and was delirious, and on the following day became unconscious. On admission to hospital on Feb. 21st, she was unconscious, restless, with marked retraction of the head, temperature 104° F., pulse-rate

124, respiration-rate 28, and double optic neuritis. Physical examination was otherwise negative except for some impairment of the percussion note at the right base where the R.M. was slightly defective. Lumbar puncture gave a turbid fluid with a sediment containing 70% polymorphs. No organisms were seen in films or grown by culture. In view of the history of the previous pleurisy and the positive tuberculin test the case was considered one of tuberculous meningitis. The child remained in the same state and died quite suddenly four days later.

At the post-mortem examination both lungs were found adherent, the adhesions being specially dense on the diaphragmatic surfaces. Both lungs were sclerosed and showed uniform dilatation of the larger bronchi, with thickened mucosa and numerous small pockets in their walls. At the

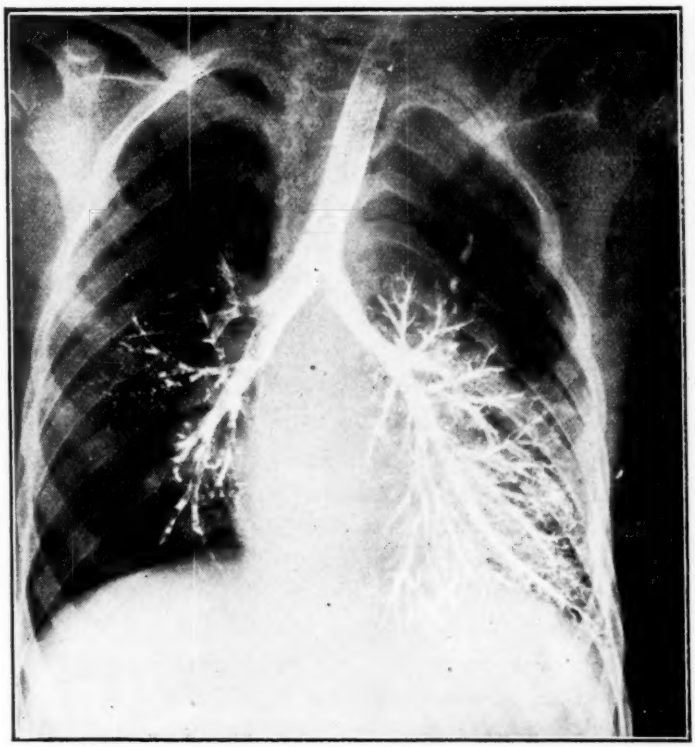

Fig. 5.—Normal bronchial tree in a case of slowly resolving pneumonia.

base of the left lung adjacent to the diaphragmatic surface was a patch of special density about one inch square containing several definitely caseous foci. The glands in the mediastinum were enlarged and caseous: one at the root of the right lung was softened, and its pus contained streptococci and pneumococci but no tubercle bacilli. In the abdomen there was evidence of a chronic plastic peritonitis with a few enlarged and caseous mesenteric glands. On opening the calvarium a small amount of purulent exudate was found over the vertex of the brain and posterior surface of the cerebellum with congestion of the meninges and some flattening of the convolutions. On cutting into the brain numerous small abscesses varying in size from that of a pin's head to that of a small nut were found scattered throughout both the grey and white matter. A hæmolytic streptococcus was cultivated from the pus in the cerebral abscesses and from the exudate on the surface of the cerebrum.

Analysis of Signs and Symptoms.

It will be evident from the foregoing case-histories which reveal so varying a symptomatology and clinical picture that the diagnosis of bronchiectasis is not always easy and that mistakes are apt to occur if one depends on ordinary physical examination. Hence in the following review of the symptomatology we have only included cases in which the condition was verified either by the use of lipiodol injection, by operation, or at a post-mortem examination.

Age Incidence and Duration.

In all we have had under observation 23 definite examples of bronchiectasis. Ten of the children were boys and thirteen girls. In age the children varied at the time of observation between twenty months and thirteen years, and the age at onset of the condition varied between seven months and ten years and four months. The duration of the ailment from the time of onset to the time of observation or death varied between three months and twelve years. In four cases the duration was less than one year, in four cases between one and two years, in two cases between two and three years, in three cases between three and four years, in three cases between four and five years, in four cases between five and six years, in one case seven years, in one case eight years and in one case twelve years.

Exciting Cause.

In all but three cases the condition could be traced to some acute pulmonary disease. In these three cases no history of an acute onset could be obtained, the story being simply that the children began to cough and spit. Simple broncho-pneumonia was responsible for eight cases, lobar pneumonia for two, pleurisy for two, bronchitis for one, measles for one, measles and broncho-pneumonia for one, influenza for one, whooping cough for two, whooping cough and broncho-pneumonia for one, and the combination of measles and whooping cough for one example. Not infrequently the initial pulmonary infection was described as severe, lasting for several weeks, and though the child did ultimately improve complete health had never been regained, cough with intermittent expectoration persisting. It is a curious fact that in spite of the frequency of the condition (we ourselves have observed fourteen cases during a period of two years—1925 and 1926) practically all writers on chronic pneumonia and bronchiectasis remark that they have never seen a case develop out of any acute pneumonia which they themselves had treated. This is all the more remarkable when one recollects how slow resolution often is both in lobar and broncho-pneumonia. We have been fortunate in observing three cases almost from the beginning (Cases 1, 2 and 6 reported in detail above), and in none did the illness seem specially severe. True, in one case (Case 6) there was the unusual occurrence of double pleurisy with effusion, but in the other two instances, one of broncho-pneumonia and the other of seeming lobar pneumonia, the initial illness was not specially severe. It was always the delayed resolution which caused anxiety. In the supposed example of lobar

pneumonia, fever, for the most part intermittent in character, persisted throughout, whereas the course of the broncho-pneumonia was afebrile during the time the child was under observation, and he seemed quite comfortable. In no instance was there a history that the insufflation of a foreign body gave rise to the condition. In our experience abscess of the lung and not bronchiectasis has resulted from the insufflation of a foreign body, e.g., a piece of tonsil during the operation of tonsillectomy.

Nutritional State.

Laennec gave as one of the cardinal features of the disease, chronicity without marked impairment of the general health. This certainly is one of the most striking characteristics of bronchiectasis. In spite of the cough and profuse expectoration continuing for years the children appear wonderfully healthy and of good colour and nutrition. Almost invariably, however, they are under height and weight for their age. In three cases the children were over height to the extent of 0.3, 2.0 and 6.6 cms., but on the average they were 7.9 cms. below Holt's standard. The loss in height did not seem to bear any relationship to the duration of the illness as the child who was 6.6 cms. over height had been ill for five years, and the child 2 cms. over height had been ill for twelve years. One child was 29 cms. below height and had been ill for seven years ; another child was 22 cms. under height and had been ill for six and a half years ; two children 13 cms. under height had been ill for three and a half and one and a half years respectively.

All the children were under weight, but on the average not to the same degree as they were under height, and it is this fact which accounts for the good nutritional appearance. The average loss in weight in twenty of our cases was only 5.58 kilos. whereas, as stated above, the average loss in height was 7.9 cms. The greatest retardation of weight was 17.7 kilos, in a child who had been ill for seven years—this child was 29 cms. under height. The child who had been ill for twelve years was only 4 kilos. under weight and another child ill for three and a half years was 8.8 kilos. under weight.

Clubbing of the Fingers.

In eleven of the cases there was clubbing of the fingers and in eleven none. In one case there is no note regarding this point. The presence or absence of clubbing did not necessarily bear any relationship to the duration of the illness as the child ill for twelve years presented no clubbing of the fingers. The average duration of the condition in those with clubbing was three years and four months, and in those without clubbing three years and five months. But the extent of the pulmonary lesion would seem to have some influence in the production of the clubbing. The mischief was extensive, e.g., involving the whole of one lung or the whole of the lower lobe of each lung in ten of the eleven cases which showed clubbing, whereas in the eleven cases without clubbing the mischief could only be described as extensive in four, being limited to one lobe or portion of a lobe in seven cases.

Cough and Sputum.

Cough, or a history of cough was present in all cases but one, the girl admitted with symptoms of meningitis in whom post-mortem examination revealed bronchiectasis in both lungs and multiple brain abscesses. The cough varied much, sometimes being very severe. It tended to occur in spasms which might last for an hour at a time. Movement or exertion would often induce a spasm. Sometimes the cough was most troublesome during the night, at other times in the morning on waking.

The cough was accompanied by expectoration in the majority of cases. In one case there was no history of sputum but on " posturing " a small amount was obtained. In four cases no sputum was obtained even on " posturing." In these latter cases the duration of the illness had been one year and five months, six months, six months, and three months ; thus in all cases of more than eighteen months' duration sputum was present. In all cases when present the expectoration consisted of more or less liquid greenish pus. As a rule the expectoration was odourless ; in only three cases could it be said to be definitely fœtid, and in these the condition had been in existence for three, three and a half and four years. In five cases hæmoptysis had occurred and, as seen from Case 1 recorded in detail above, death resulted from a severe hæmoptysis probably due to the rupture of an aneurysm in one of the bronchiectatic cavities. It is not infrequent, however, on " posturing " so as to empty the bronchiectatic cavities to see the last of the sputum expelled slightly tinged or streaked with blood, and we learned to appreciate this as a sign that for the time being no more sputum could be expelled. The amount of sputum brought up at one time and during the twenty-four hours varied much. In some cases as much as two and a half oz. was expectorated at one time whereas in other cases it was with the greatest difficulty that even one drachm would be obtained. During the twenty-four hours we have seen as much as eight ozs. expectorated by one child, whereas in another the daily expectoration would only amount to one drachm. The daily amount of sputum expectorated did not seem to bear any relationship to the extent of the mischief.

Physical Signs.

The physical signs in the chest varied much in this series. In some cases there was shrinking of the whole of one side of the chest with pulling over of the heart so that the apex beat was situated in the axillary line, raising of the diaphragm and dense dullness to percussion all over the affected side. If the accompanying pulmonary fibrosis were limited to one lobe, the shrinking of the side and dullness to percussion were limited to the apex or base. In some cases where the fibrosis and accompanying bronchiectasis were limited in extent and deeply situated there was no appreciable change in the shape of the chest and no dullness to percussion.

Auscultation of the affected side of the thorax often revealed only a defective R.M. On the other hand the R.M. in some cases was unduly loud and tubu-

lar in character and in others amphoric or cavernous. If the bronchiectatic cavities were filled with secretion nothing pointing to cavity formation might be audible : the amphoric character of the R.M., however, sometimes became intense after evacuation of the secretion by getting the patient to cough while inverted, and in any doubtful or suspected case this procedure should never be omitted. When the amphoric character of the R.M. was intense it was as a rule limited to one area, most frequently the neighbourhood of the angle of the scapula, but on occasions this change in the R.M. has been heard at the apex and in the axilla. It has been remarkable that the signs of cavity would be audible only at one base though lipiodol injection or post-mortem examination

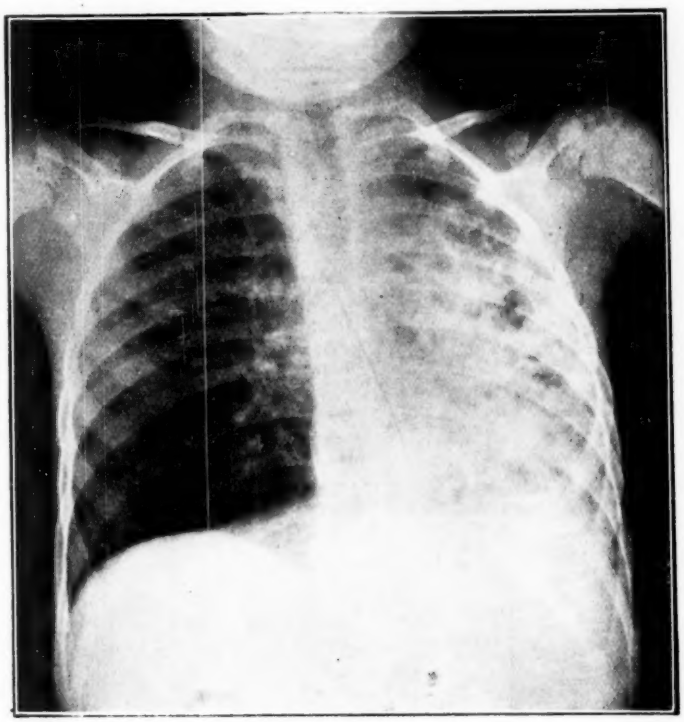

Fig. 6.—Case 9. Honeycomb appearance in chronic pneumonia suggesting cavity formation.

revealed the mischief at both bases or widespread throughout the whole of one lung. (*See* Cases No. 4 and 14 in Appendix.) Not infrequently the whispered voice was well conducted to the area where the amphoric R.M. was audible, but this phenomenon was not so frequent as the hollow character of the R.M.

Radiological Examination.

X-ray examination of the chest, like physical examination, revealed most diverse pictures, varying between a dense shadow all over one side of the chest to a slight and questionably abnormal reticulated shadow at one base. The varying picture obtained would seem to depend on the extent of the fibrosis of the lung. Sometimes the shadow has the appearance of a honeycomb suggesting cavity formation (*See* Fig. 6) or dilatation of the bronchi, but

experience with lipiodol injections shows that this conclusion cannot always be drawn from such an appearance. At times the abnormal shadow at the base of one lung has looked like ghosts of dilated bronchi and the lipiodol injection has verified this assumption (*See* Figs. 7 & 8). In the presence of extensive fibrosis a characteristic feature is the displacement of the trachea and the heart to the affected side. (*See* Fig. 9). We are convinced, however, that if one were to depend entirely on the simple X-ray photograph mistakes would frequently be made—bronchiectasis would be diagnosed when it did not exist and its presence missed because of the absence of an unequivocal picture.

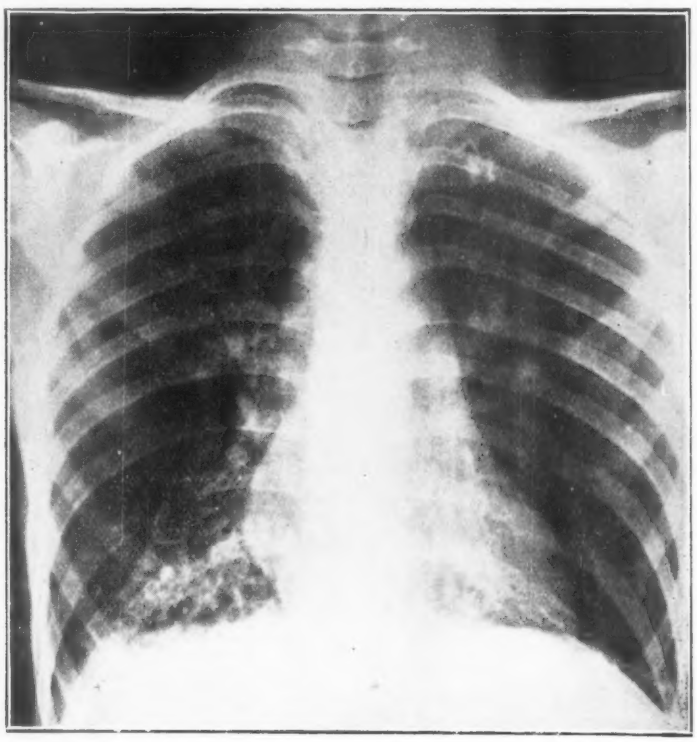

Fig. 7.—Case 14. Honeycomb appearance at right base and ghosts of dilated bronchi at left base.

Hence, if one wishes to be certain of the presence of this condition recourse must be had to an X-ray examination of the chest after the instillation of lipiodol into the bronchial tree. By this means, as is evident from the cases detailed above and the various X-ray pictures, the conformation of the bronchi is clearly shown so that it is apparent whether the various branches taper gradually towards their terminations or whether the bronchi are dilated either in their length (tubular bronchiectasis Figs. 1, 9 and 10) or merely towards their extremities (saccular bronchiectasis Figs. 2, 8 and 9). As previously mentioned the exact distribution of the dilatation is only to be appreciated in this way.

In following the different types of cases injected we have been struck with the varying behaviour of the lipiodol. Not only the distribution of the oil but the rate of its disappearance depended on whether dilatation of the bronchi existed or not. In the presence of bronchiectasis the lipiodol was usually, so far as that portion of the lung was concerned, entirely limited to the lumina of the bronchi and was present as dense and large oblong or circular shadows, whereas in the healthy portion of the lung, it was usually more widespread and present as a fine powdering as if it had gained entrance to the pulmonary alveoli. (Fig. 4.) In fact, this varying picture was so characteristic that

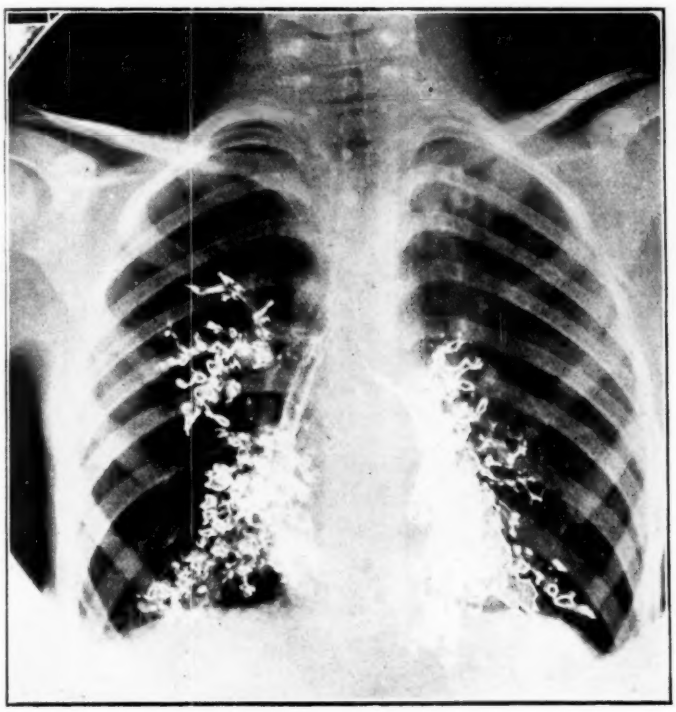

Fig. 8.—Case 14. Sacculated bronchiectasis at both bases.

we learned to utilise it as evidence for or against bronchiectasis. It was also striking how the rate of disappearance of lipiodol from the lung varied. The lipiodol disappeared much more quickly from the bronchiectatic portion of the lung than from the normal portion. In the former all evidence of lipiodol would be gone within 7 to 10 days whereas the fine powdering effect of the oil apparently in the alveoli would persist for as long as three to eight weeks.

Localisation of the Disease.

One of the most striking features of this disease is its distribution, a fact already referred to and one of great value in the differential diagnosis between bronchiectasis and pulmonary tuberculosis. Bronchiectasis shows a great tendency to be limited to one lung or even one lobe of a lung, to involve the

base of the lung rather than the apex, and to attack the left lung much more frequently than the right, all of which points are in marked contrast to the behaviour of tuberculosis. In fourteen cases the left lung alone was the seat of the disease, in four cases the right lung alone and in five cases both lungs. In none of our cases was the apex of the lung alone involved and in every instance in which the apex was attacked the whole lung was implicated.

This distribution is exactly what has been found by previous writers on chronic pneumonia, which, as we have previously said, for all practical purposes means bronchiectasis. Clark, Hadley and Chaplin ([1a]) found in their series

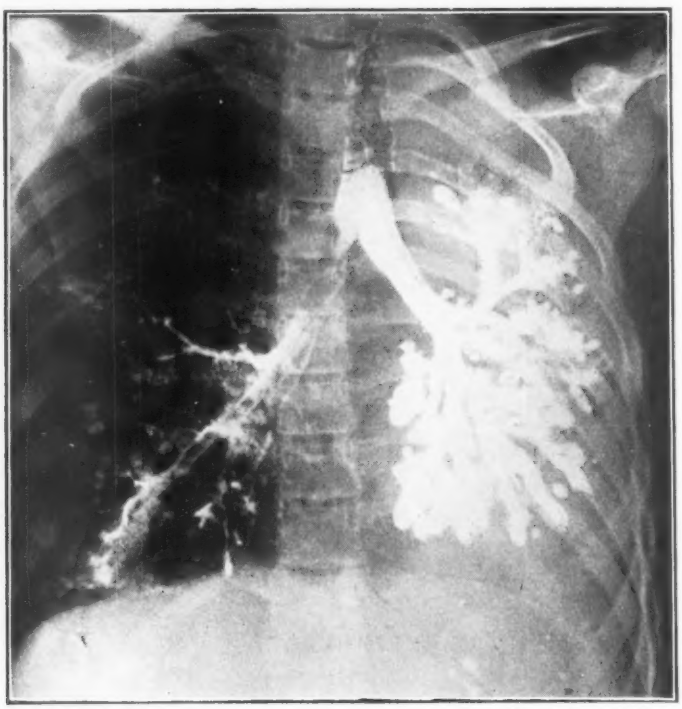

Fig. 9.—Case 22. Extreme degree of tubular and saccular bronchiectasis in pneumonia of left lung.

of forty-five cases the left lung involved in twenty-five, the right in fifteen and both in five. Fox([7]) found the left lung the seat of the disease in twenty-two cases and the right lung in ten, and McNeil([8]) in his series of five cases observed the left lung diseased in four and the right lung in one. Fox quotes the apex of one lung affected in three cases and both apices in three, but in two of these the affection was tuberculous.

Technique of Injection of Lipiodol.

In view of the different methods of introducing lipiodol into the bronchial tree some remarks may be permitted regarding our experience with the various techniques. The iodized oil can be introduced into the trachea either by means

of a tube through the glottis (largyngeal syringe or bronchoscope) or by means of a needle inserted through the crico-thyroid membrane. In the case of an adult it may be comparatively simple to use a laryngeal tube. In the child, on the other hand, the glottis is small and we have found it exceedingly difficult to get the pharynx and larynx sufficiently anæsthetised to permit of the operation, and any results obtained in this way have been unsatisfactory. We have seen some quite good results obtained thus in the adult but even in them the pictures were never so good as those obtained by crico-thyroid puncture. In any case it seems to us that in the young child a general anæsthetic is

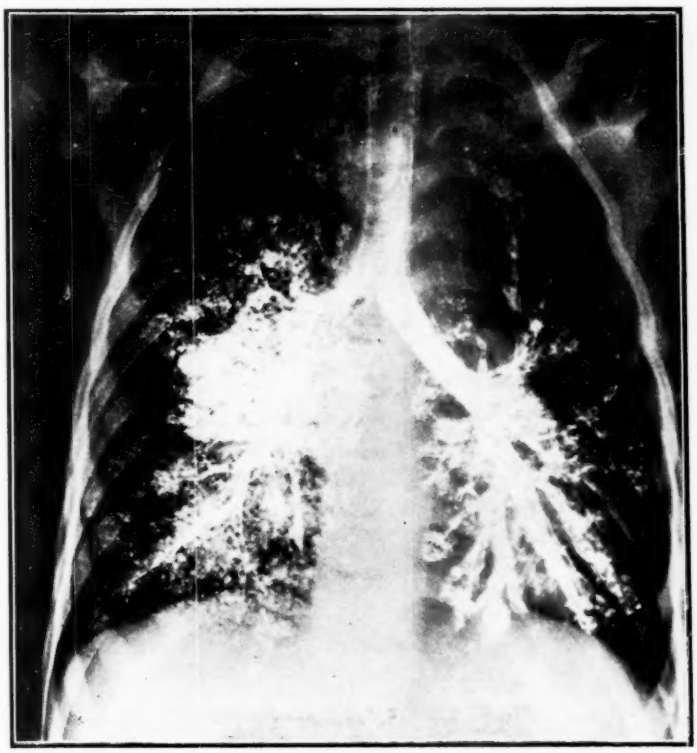

Fig. 10.—Case 19. Tubular bronchiectasis in left lower lobe.

essential for psychic reasons apart altogether from the physical discomfort of the operation. In older children we have found it possible to perform the operation of crico-thyroid puncture under a local anæsthetic, but the parts in a child are very soft and it is difficult to get the child to avoid any movement or act of swallowing so that the seat of the operation may be kept at rest. With the child under a general anæsthetic, however, it is comparatively simple to enter the trachea through the crico-thyroid membrane. The needle which we have found most suitable is one with a diameter of 1·5 mm., curved and mounted with a flange like a tracheotomy tube and provided with a stilette. The stilette may project beyond the needle when it has a blunt end just as in the

case of an ordinary canula and trochar but the form employed in needles for lumbar puncture is better : here the needle is sharpened to an angle of 45° and the stilette similarly angled to become flush with the needle point. Before giving the anæsthetic it is a wise precaution to empty the bronchiectatic cavities as completely as possible by inverting the child and inducing him to cough. When the child has been completely anæsthetised the thyroid cartilage is grasped between the finger and thumb of the left hand, the crico-thyroid membrane identified, and the needle with stilette *in situ* inserted in a backward and downward direction. If a large needle is employed one learns immediately on the withdrawal of the stilette if it is in the trachea from the rush of air in and out of the tube just as occurs after the insertion of a tracheotomy tube, but with the size of needle recommended the lumen becomes so easily blocked with the purulent secretion in the trachea that no air can pass. We have found, however, that this point can be easily settled by attaching a syringe to the needle and applying suction : if the needle is in the lumen of the trachea air can be readily withdrawn and also introduced. After deciding that the needle is properly in the lumen of the trachea one or two ccm. of a 4% solution of novocaine are injected to counteract any tendency to cough and then the syringe filled with the lipiodol (15 to 30 cc.) is attached and the oil slowly injected. The larger the amount of oil employed the better are the various branches of the bronchial tree demonstrated—in infants of 1 year we have injected as much as 25 ccm. The entrance of the oil into the bronchial tree is aided by elevating the shoulders slightly while the oil is being injected but it is not necessary to turn the child on his side to facilitate the flow into one or other lung. In our experience the bronchiectatic portion of the pulmonary system possesses an affinity for the oil, due probably to the diminished expiratory efforts and resistance in these bronchi. The lipiodol is a very viscid fluid and unless it is warmed will not run through the size of needle recommended, especially when it is bent in the shape of a tracheotomy tube. In consequence a metal syringe which can be easily heated is recommended, and preferably one provided with a piston rod which is worked by a screw so that great pressure may be exerted. Immediately after the injection an X-ray examination of the chest is made, and for this reason it is advantageous when possible to carry out the whole operation in the X-ray department, and in the case of children an instantaneous apparatus is essential for the production of sharp pictures. As a rule some of the lipiodol will have been coughed up and swallowed and will be seen in the stomach, but sufficient will have remained in the bronchial system to demonstrate any abnormality in the calibre of its various components.

Course of the Disease.

Various are the opinions held regarding the course of the disease. Many authorities are non-committal on the question, but others again are very definite in the expression of their view. Nobecourt[9], for example, states quite explicitly that recovery not infrequently takes place and explains this result by suggesting that the dilatation of the bronchi ceases to increase after a time, and that as the

lung grows the bronchi ultimately come to have the normal proportions. This hopeful view has been recently re-affirmed by Thursfield and Paterson[10] during a discussion of the question before the Royal Society of Medicine.

In our experience the condition does not show any marked tendency to heal. Cases in which the history is of more than five years' duration have shown on the whole a tendency to get worse. And from the cases which we have seen come to post-mortem examination we have the greatest difficulty in understanding how recovery can take place. The naked-eye appearance of the section of the lung in some of the cases looked like the section of a sponge and suggested rather a cystic kidney or hydatidiform mole. In this matter of prognosis we would again remark on the uncertainty of diagnosis of the mischief by ordinary physical examination, at least in many cases. This seems to us to be at the very root of the whole question. We do not believe that it is possible, unless with the aid of lipiodol, to form either a definite opinion as to its presence or a correct estimate of its extent. Hence to our mind the truth regarding the course of this disease is reserved for the future. We have seen, as Case 6 detailed above shows, a slowly resolving pneumonia which ultimately cleared up simulate closely bronchiectasis. We were fortunate, however, in demonstrating by means of lipiodol that there was no dilatation of the bronchi, but without this advantage the case might have been classed as an example of recovery from bronchiectasis.

That patients with bronchiectasis may live for many years without showing any severe impairment of the general health is undoubted. This we have seen from our limited survey and most writers record examples attaining a ripe age though suffering from a marked degree of the condition. It is striking, however, while reviewing the literature to notice what a large proportion of the patients are children or adolescents and to learn from conversations with physicians whose clientele is recruited more from the adult than the child population that they seldom meet with the disease. Do these facts signify recovery from the condition or early death and a shortening of life ? The latter view was that held by Sir Andrew Clark and Wilson Fox. Both these authors were discussing at the time chronic pneumonia, which they admitted and we ourselves have stated practically means bronchiectasis. Of Clark's series of forty-five cases twenty-seven or 60% were under twenty years of age, and he put the average duration of life after developing the disease at 11.8 years. Of Fox's series of thirty-eight patients he found that twenty-two or 58% died under forty years of age, and the duration of the disease in seventeen of these was only eleven years.

The cause of death may be septic broncho-pneumonia, gangrene of the lung, hæmorrhage or cerebral abscess, events which may occur at any time.

It is remarkable in view of the supposed tendency for tuberculosis to occur in the fibrotic lung of pneumoconiosis that chronic pneumonia and bronchiectasis should be accompanied so seldom by tuberculosis. This fact has already been remarked upon by Clark and McNeil and would seem to support Oliver's [10a] contention that the pneumoconionic lung is not specially

susceptible to a tuberculous invasion. *A priori* one has difficulty in understanding how dense fibrous avascular tissue should permit of easy infection and McNeil, while discussing this question, refers to the disappearance of lymph channels in the fibrotic areas as raising a barrier to infiltration by the tuberculous process.

Of our own series of twenty-three patients, nine died, two from septic pneumonia, one of which had in addition early tuberculosis, one from hæmoptysis, one from multiple cerebral abscesses, one from tuberculous meningitis and four as a result of operation. One patient died during the operation for pneumectomy, one two days after the same operation from hæmorrhage through slipping of the ligature at the root of the lung, and two some time after the fixation of the lung to the thoracic wall and incision of the cavities for drainage.

Ætiology.

Though Laennec[2] gives a very good account of the clinical history and pathological picture of bronchiectasis he expresses no opinion regarding the cause. It was left to Andral writing in 1824 to make the first suggestion. Andral[3] considered that inflammation of the bronchi and the consequent diminished resistance of the walls makes them yield when submitted to forced inspiration or expiration as during the spasms of coughing. This same view was expressed in 1837 by Stokes[11] of Dublin who contributed the first full account of the disease in English. He believed that loss of elasticity, contractility, and ciliary movement, were the important factors in its ætiology, and held that in all cases the starting point was bronchitis. This is a view which has been resuscitated at different times since and even to-day finds adherents.

Corrigan[12], one other of that famous group of Dublin physicians, noted for the first time in 1838 another and probably the most important factor in the causation of bronchiectasis. Corrigan considered cirrhosis of the lung analogous to Laennec's cirrhosis of the liver and put forward the view that dilatation of the bronchi was due in part to the contractile processes going on in a cirrhotic lung, and in part to the expansile action of the chest wall. His views are classically stated as follows: "If there were but one bronchial tube with contracting fibro-cellular tissue placed around it, then the contracting tissue would, as in the instance of stricture of the œsophagus or rectum cause narrowing of the tube, but where there is, as in the lung, a number of bronchial tubes and the contracting tissue not placed around the tubes but occupying the intervals between the tubes, then the slow contraction of the tissue will tend to draw the parietes of one tube towards the parietes of another and necessarily dilate them."

Hamilton[13] many years later in a discussion of Corrigan's theory mentioned the further factors of pleural adhesions and the rigid chest wall, which in his opinion by giving a fixed point of resistance increase the pulling effect on the bronchi. As he says "both the chest wall and the bronchus will be influenced, but the former, being much the stronger of the two and representing an arch

with its concavity towards the point of traction, will be influenced to a less extent than the thin wall of a bronchus with its convexity towards the point of traction." Hamilton, however, considered that increased inspiratory and expiratory efforts with the accumulation of secretions in the bronchi, as suggested by Stokes, might also play a part in those examples following bronchitis, when the weakened bronchial wall in its thinned state would be specially susceptible to increased pulmonary pressure. This view has been embraced by many of the more recent writers, and some of these, e.g., Lebert[14] and Gairdner[15] go so far as to deny fibrosis of the lung as in any way contributory. Grainger Stewart[16] compares the production of bronchiectasis to that of an arterial aneurysm or staphyloma of the eye. Some authors again have introduced a nervous element into the question. Loss of nerve control is the term used by Lebert and Biermer[17].

From a study of our own material we incline to the view that pulmonary fibrosis and pleural adhesions take the chief share, if not the sole burden, in the causation of bronchiectasis. It must be recalled that post-mortem examination of examples of broncho-pneumonia of some weeks' duration not infrequently reveals quite definite, though moderate, bronchiectasis in the pneumonic areas, histological examination of which may show an overgrowth of connective tissue. Of this we have seen many examples, which have left us with the impression that, if these children had been able to withstand the more acute phase of the mischief, fibrosis with clinical bronchiectasis would have resulted.

It is difficult to differentiate between the relative importance of fibrosis and pleural adhesions, because though the history more often suggests broncho-pneumonia as the primary lesion, both are frequently, and in fact in our post-mortem material both invariably were, co-existent. The fact, however, that the disease usually sets in at a period of life when simple pleurisy is so rare, rather militates against the hypothesis that pleurisy *per se* is a common ætiological factor.

It is interesting to note that in a large proportion of the cases the ætiological broncho-pneumonia was secondary to measles and whooping cough, but we can corroborate the statements of Clark and Fox that both primary broncho-pneumonia and lobar pneumonia may be responsible for its production. In the case of pleurisy (Case 7) there was, however, a superimposed fibrosis of the lung.

We agree with Rapp in his scepticism that bronchitis, at least *per se*, can be an ætiological factor. Surely if uncomplicated bronchitis played any prominent part in causing the condition bronchiectasis would be a much more common finding than it is. The fact, too, that the dilatation is most frequently limited to one lung and to only one part of one lung, is surely against the hypothesis that it can be due to a condition which is usually generalised. Nevertheless, not only in our own series but also in those of other writers, a history is sometimes obtained that bronchitis was the starting point of the patient's malady. In our own series this was so in one case, but this patient

was an infant at the time when the difficulty of differentiating between bronchitis and broncho-pneumonia is well-known.

No more does the hypothesis of increased intra-pulmonary pressure appeal to us as in any way responsible for dilatation of the bronchi. From what we have seen of bronchiectatic lungs post-mortem they would seem, on account of the fibrosis, to be in a state to withstand pressure better than in health. Further as the diseased lung can neither expand nor contract so efficiently as in health even if there were a stricture, as some have suggested, the *vis a tergo* (expiratory effort) would be distinctly below normal. Many writers who support this hypothesis remark on the association of the condition with severe coughing but as we have shown in our remarks on the symptomatology coughing may be entirely absent. It is more probable that the cough is dependent on the bronchiectasis rather than that the bronchiectasis is dependent on the cough.

To our mind the only feasible explanation of the condition is the fibrosis of the lung, as first suggested by Corrigan, with the added influence of pleural adhesions, as first pointed out by Hamilton, since without doubt by providing a fixed point for the contracting fibrous tissue these adhesions increase the traction force of the intra-pulmonary fibrosis.

The radiograms were all taken by Dr. D. Campbell Suttie, Superintendent, Royal Hospital for Sick Children, Glasgow, to whom we have much pleasure in expressing our thanks.

APPENDIX.

Synopses of cases of bronchiectasis analysed in this paper.

No. 1. S.E. (Case 1, p. 73).

No. 2. I.N. (Case 2, p. 74).

No. 3. A. McM. (Case 3, p. 75).

No. 4. R.R. (Case 4, p. 76).

No. 5. A.T. (Case 5, p. 77).

No. 6. I.H. (Case 6, p. 78).

No. 7. C.H., girl, aged 5 years, took ill at three and a half years with broncho-pneumonia and pleurisy. She had a cough with a fœtid muco-purulent expectoration. She weighed 14.1 kilos. and had definite clubbing of the fingers. Physical signs were those of fibrosis of the whole left lung and cavity at the base. Von Pirquet was negative. Operation and death two days later through slipping of the ligature at the root of the lung and severe hæmorrhage. P.M. :—Whole left lung fibrosed with generalised bronchiectasis.

No. 8. A.D., girl, aged six years and one month : at three years without apparent cause commenced to cough and spit up muco-purulent material. Cough and spit gradually increased and spit became fœtid : ultimately half a teacupful would be brought up at one time, the last portion expectorated being blood-tinged. Fingers had been noticed to be clubbed for two years. Signs of fibrosis of left lung. After posturing R.M. which had been diminished became amphoric at angle of left scapula. Child died under chloroform given for proposed pneumectomy. P.M. :—Left lung sclerosed throughout with great dilatation of bronchi. Right lung healthy.

No. 9. C.C., boy, aged four years and ten months. Had measles and whooping cough at one year and cough and purulent spit since then. The cough and spit are worse in the evening. There was no fever and the von Pirquet was negative. Height 97 cms.; weight 13.1 kilos. Expansion of left lung impaired, note dull all over left side back and front and in lateral region. R.M. deficient in axilla where it was tubular. On posturing three drachms purulent sputum obtained and R.M. highly tubular in axilla and lateral region. Fingers clubbed. X-ray of chest showed honeycombed shadow all over left side with heart drawn to left (Fig. 6). Lipiodol injection revealed bronchiectasis at left base.

No. 10. A.P., boy, aged ten years. Had influenza at six years and since then cough cyanosis, and dyspnœa. Admitted to hospital acutely ill with fever, intense cyanosis and dyspnœa. Fingers and toes clubbed. Breath foul. Percussion note dull at both bases. R.M. tubular at right scapular region. X-ray examination of chest showed generalised shadows extending out from both roots. P.M. :—Generalized bronchiectasis both lungs with gangrene of small area in left lower lobe.

No. 11. J.F., girl, aged four and a half years. Had whooping cough complicated by broncho-pneumonia at three years and had never been well since, cough with profuse purulent expectoration coming on in paroxysms in morning on waking. Had been seen three months after onset of illness when physical and radiological signs were those of fibrosis of whole of left lung. At four and a half years moderately healthy looking child. Height 100 cms. Weight 14.4 kilos. Finger tips clubbed and cyanosed. Left chest shrunken ; heart drawn over to left side; dullness to percussion all over left side with tubular R.M. at apex and amphoric R.M. at angle of scapula. Child expectorated about 3 ozs. of sputum daily. Von Pirquet positive. Sputum negative for tubercle bacilli. X-ray of chest showed shadow all over left side with cavitation at apex. Lipiodol revealed bronchiectasis but limited to left lower lobe.

No. 12. T.M., a boy, aged nine years, came under observation on May 14th, 1925. Had whooping cough at the age of two and a half years and ever since a cough with a profuse yellow spit. Five months previously he had developed a right-sided lobar pneumonia followed by empyema which was drained and healed satisfactorily, but as the cough persisted and in fact was becoming worse, and the purulent expectoration was more profuse, he was referred to the medical side for an opinion. On first coming under our observation he was a healthy looking boy but much under height and weight, measuring 105 cms. and weighing 24 kilos. He had a good colour and there was no clubbing of the fingers. The von Pirquet tuberculin reaction was negative. Examination of the chest revealed an impaired note at the left base with a tubular R.M. at the angle of the scapula. The right chest was clear. After inversion and coughing up half an ounce of muco-purulent expectoration devoid of all odour the percussion note at the left base became clearer, the R.M. definitely amphoric in character, and whispered pectoriloquy could be appreciated. An X-ray photograph of the chest showed a slight shadow at the left base and after the injection of lipiodol extensive dilatation of the bronchi in the left lower lobe. This boy was in residence in hospital for eight weeks during which time his condition remained stationary, the daily amount of sputum varying between one and two ounces. The temperature was normal during the whole residence.

No. 13. R.S., boy, aged eight years. Developed cough and spit at age of four years—gradually increasing in severity so that one half teacupful would be expectorated at one time. At seven years developed whooping cough and since then symptoms worse and spit frequently streaked with blood. Dull to percussion at left base with tubular R.M. and bubbling râles. After posturing one ounce of fluid muco-purulent material streaked with blood expectorated when dullness at base disappeared and R.M. became amphoric in character. Operation for incision and drainage of cavities. Died three months later.

No. 14. W.M., a boy, aged seven years. Had broncho-pneumonia at age of two years when he was ill for four months, since then cough and spit with recurrent attacks of fever. Spare

delicate looking boy. Height 124 cms. Weight 17.5 kilos. Slight clubbing of the fingers. Dullness to percussion in right interscapular region with tubular R.M. at angle of scapula and whispered pectoriloquy. Moist râles at both bases. X-ray showed increased hilum shadows in both lungs and honey-comb appearance at both bases. (Fig. 7). Lipiodol revealed extensive saccular bronchiectasis at both bases. (Fig. 8).

No. 15. J.C., boy, aged six years. Developed whooping cough at one year and had cough and spit ever since. Contracted measles at three years and since then cough and spit worse. Spit latterly frequently streaked with blood and at times definite hæmoptysis. Seen at age of four years when he was noted to be undersized (height 89 cms. and weight 11.9 kilos); there was no cyanosis and no clubbing of the fingers; von Pirquet tuberculin reaction positive. Chest pigeon-shaped with dullness at right base behind and in right lateral region and abundant moist râles at both bases. X-ray revealed shadows at both bases and appearance suggestive of cavity at right base. On second occasion, i.e., when six years of age, was still troubled with cough and greenish spit, especially annoying at night or after violent exercise; he measured 102 cms. and weighed 15.4 kilos.; there was dullness to percussion at left side back and front; X-ray examination revealed slight honeycomb shadows at both bases with suggestion of cavity at right base. Lipiodol revealed extensive tubular dilatation of bronchi apparently in left lower lobe. Otherwise conformation of bronchi was normal.

No. 16. M.B., girl, aged eight years. Since pneumonia one year previously child had never been well being troubled with cough and breathlessness on exertion. Admitted to hospital acutely ill with fever, rapid respirations and cyanosis of six days duration. She was a much undersized child weighing 13.8 kilos., markedly cyanosed and presenting definite clubbing of fingers. Cough was very troublesome and was accompanied by profuse purulent expectoration which on examination did not reveal any tubercle bacilli. Right side of chest, back and front, was dull to percussion with a diminished and intensely tubular R.M. over scapular region. Abundant râles all over left side. Child continued very ill and died six days after admission. At P.M. examination right lung was found generally adherent, sclerosed and the seat of diffuse cylindrical bronchiectasis: the left lung was enlarged and emphysematous with scattered throughout areas of suppuration. Mediastinal glands enlarged with central areas of suppuration. Microscopic examination of foci in left lung revealed giant cells and caseation.

No. 17. J.F., boy, aged nine years. Had influenza at three years and measles and whooping cough at four years, since when he has been troubled with a cough and subject to febrile attacks. Came under observation during a febrile attack. Small underweight boy, 108 cms. and 17.2 kilos. Colour good and no clubbing of fingers. Von Pirquet reaction positive. Dull at right base behind below angle of scapula with very deficient R.M. After posturing 1 drachm thick purulent sputum devoid of all odour evacuated and dulness at right base became less intense and R.M. tubular; X-ray revealed widening of mediastinum and shadow at right base and after lipiodol dilatation of bronchi in right lower lobe.

No. 18. J.B., boy, four years. Took ill six months previously with acute illness characterised by cough, dyspnœa and vomiting. Seen one month later when dullness detected over left chest with much moist clicking râle at base. X-ray of chest revealed shadow throughout left lung with heart pulled over to left. Condition diagnosed as unresolved pneumonia. Seen again five months later with a height of 94 cms. and weight of 13.75 kilos., a troublesome cough, but no history of spit, dull to percussion all over left side of chest, amphoric R.M. in axilla and moist râle all over. X-ray picture showed shadow throughout left side with slight tubular clear areas suggestive of bronchi towards base and honey-comb appearance at apex. After lipiodol saccular dilation of bronchi throughout left lung.

No. 19. A.S., a girl, aged eight years. Came under observation on account of cough and wasting of eight months' duration. History of broncho-pneumonia at fifteen and twenty-seven months of age, whooping cough at two and a half years with slow recovery, and

broncho-pneumonia again at four and a half years when she was very ill; has never been well since. Eight months previously commenced to complain of pain in left side and a cough which was worst on waking in the morning and was accompanied by a yellow spit. She was an undersized child (109 cms.) and weighed 15.2 kilos. Slightly cyanosed, but no clubbing of the fingers. The von Pirquet reaction was negative. Percussion note impaired all over left side of chest but definitely dull over back with amphoric R.M. and crackling râles at the base. On posturing two drachms odourless purulent expectoration evacuated when R.M. at base became intensely amphoric. X-ray showed shadow at left base with heart pulled to left and after lipiodol dilatation of bronchi in left lower lobe. (Fig. 10).

No. 20. E. McC., a girl, aged three years, admitted to hospital with cough and purulent spit. Date of onset unknown. She was an undersized child weighing 10 kilos. with cyanosis and clubbing of the fingers. Chest was dull to percussion all over right side back and front with at base behind a definitely amphoric R.M. Sputum examined on several occasions for tubercle bacilli but with negative result. X-ray examination of the chest revealed picture of chronic pneumonia throughout right lung. Child was submitted to operation for incision and drainage of cavities but died two days later. P.M. examination refused.

No. 21. N.D., a girl, aged twenty months, admitted in a semi-conscious condition, irritable, with slight fever and symptoms of meningitis, which lumbar puncture confirmed and showed to be tuberculous in nature. There was a history that she had had pneumonia three months previously and that there had been a troublesome morning cough since but no spit. Physical examination of the chest revealed dullness in right lateral region but nothing abnormal on auscultation. X-ray examination of the chest showed a shadow at right base with a honey-comb appearance. Child died one week after admission to hospital and at P.M. examination there was found fibrosis of right middle and lower lobes with extensive bronchiectasis: tuberculous meningitis confirmed.

No. 22. J.R., girl, aged eleven years, had been a healthy child till two years prior to coming under observation. At that time had tonsils and adenoids removed and was immediately afterwards very ill with broncho-pneumonia being confined to bed for four weeks. Since then cough and purulent spit, which have steadily increased in severity. She was a spare and undersized girl; height 132 cms. and weight 26.76 kilos. Colour good but fingers clubbed and cyanosed. Cough troublesome with profuse muco-purulent expectoration devoid of all fœtor. Left side of chest retracted, dull to percussion all over back and front with heart drawn over, apex beat being in fifth space four and a half ins. to left of middle line. R.M. tubular all over left side and amphoric at base behind. Whispered voice well heard all over left side. X-ray examination of chest revealed dense shadow all over left side with heart and trachea displaced to left. After lipiodol injection through the crico-thyroid membrane under a local anæsthetic very extensive bronchiectasis (tubular and saccular) throughout left lung was apparent. (Fig. 9.)

No. 23. P.R., girl, first came under observation on October 18th, 1922, at age of seven years and ten months with history of cough since before she was one year old. At three years she had broncho-pneumonia and cough has been worse since, coming in bouts and lasting for as long as an hour at a time. No history of sputum. Had pneumonia again eight months ago and, according to the doctor who attended her, the left lung did not clear up. On admission to hospital at this time she was an undersized child measuring 102 cms. and weighing 12.14 kilos. The left chest was found smaller than the right with dullness to percussion at left apex and over left lower lobe behind where R.M. was defective but tubular. An X-ray examination of the chest revealed dense shadow all over left side of chest with a somewhat honey-comb appearance at apex and heart and trachea drawn over to the left.

She was seen again on June 4th, 1925, when aged eleven and a half. During the interval the cough had persisted and there was still no history of sputum but on posturing two drachms of a thick muco-purulent odourless expectoration was obtained. She weighed 19.11 kilos.

and measured 141.5 cms. There was still dullness all over the left side with R.M. amphoric in the lateral region. X-ray examination on this occasion still showed dense shadow all over left side with cavitation at apex and heart and trachea drawn over to the left. Injection of lipiodol demonstrated definite bronchiectasis in left lower lobe.

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PYELITIS IN INFANCY; A Pathological Study.

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The clinical picture of "pyelitis in infancy" is so familiar to anyone dealing with children, and is so glibly spoken of in text-books and medical journals, that one would imagine the disease had a definitely established pathological basis. This is not the case. It was in an attempt to establish this basis that the present study was undertaken. In the presentation of the data I shall give first the evidence as to the site and nature of the lesion as shown by the pathological observations of previous authors, and by my own studies; then that derived from surgical procedures; and, finally, the little so far obtained by cystoscopic methods. I shall then deal with less completely certain ætiological factors. The subject has been confined to a discussion of the disease as it occurs in infants of two years and less: cases of obvious congenital malformation and those complicated by stone have been omitted.

I. Historical.

Escherich[1] is generally given credit for having first introduced the conception of pyelitis as a clinical entity into pediatrics. Actually he described, in some lectures given in 1895, several cases of pyuria occurring in girls of from seven to nine years of age, and, arguing from analogy to the known condition in adults, he concluded that these were cases of cystitis. The following year Finkelstein[2] reported eight autopsies on infants mostly under one year of age, and deduced from his findings that the lesion present was a primary pyelitis. Yet he reported only one microscopic examination, which, remarkably did not include the renal pelvis. In 1897 Trumpp[3] reported Escherich's cases again and added several of his own, together with autopsies. In only two cases were lesions found in the urinary tract, and in these no microscopic examination was reported.

Following this there was a break of ten years during which controversy raged, but no proof was forthcoming. In 1907 Caccia[4] reported fifteen cases, but only one autopsy. In the brief record it is stated that the patient was a boy of nine months, in whom pyuria accompanied a bronchopneumonia, and that, at autopsy, parenchymatous nephritis and thrombosis of the left renal vein were found. The next year Zahorsky[5] reported a fatal case in a girl of eight months who, at autopsy, showed multiple ulcers of the ureters. No microscopic examination was recorded. In 1909 Thomson[6] reported twenty-five cases; McDonald[7] at the same time describing in great detail the pathological findings in two of Thomson's patients who died. These were two boys of four and seven months respectively. In both cases there were extensive focal and diffuse suppurative lesions in the kidneys, associated with doubtful catarrhal changes in the pelves and ureters, and still less in the bladder. The submucosa of these latter organs showed perivascular mononuclear infiltration. In the first case the lesion was bilateral. In both colon bacilli were present. This is the first clear description of the lesion which we possess, but both Thomson and McDonald looked upon these as exceptional cases and missed their true significance.

The reader is referred to this article for several excellent photomicrographs, and also a good coloured plate of a gross specimen. In the same year West[8] reported a case in a girl of ten months, occurring as a sequel to pneumonia. The microscopic examination was made by McCallum, who reported the condition as being a suppurative nephritis. The renal pelves were not mentioned.

In 1910 Jeffreys [9] reported sixty cases of bacilluria, with four autopsies in children under two years. The pathological reports were quite incomplete, there being no microscopic record in two, and no mention of the pelves in the other two. That year Thiemich[10] made an important contribution to the subject. Among his cases he reported three autopsies on boys of two and a half, five and a half, and six and a half months, and four on girls of three, five, seven and eight months. In six of these there were found extensive suppurative lesions of both kidneys, together with a normal pelvic mucosa. In some the pelvic submucosa appeared thickened, or contained momonuclear cells in abnormal amount. One showed, in addition, infiltration of the submucosa of the fundus of the bladder with mononuclear cells. In the seventh patient, a girl of seven months, the pathological lesion was confined to the bladder. Four of the six cases with kidney lesions suffered from a preceding upper respiratory infection. Unfortunately Thiemich did not examine the urine or kidneys bacteriologically.

In 1916 Cabot and Crabtree[11], in discussing non-tuberculous kidney infection, mentioned the case of a girl of four months, who post mortem showed apparently a true pyelitis without renal involvement. The bladder and ureters were not mentioned in the protocol.

In 1918 Wieland[12] gave his experience with the pathological findings in the disease. "Unfortunately," he wrote, "the autopsy throws little light on the mode of infection. Mild cases can heal without leaving any anatomical trace. We have been able repeatedly to convince ourselves of this by the autopsy of patients who have had a mild pyelitis, and who have died of some intercurrent disease. Neither macroscopic nor microscopic change could be demonstrated in the pelves or kidneys of these children, which suggested a preceding pyelitis or pyelonephritis. In acute fatal cases the pelves and ureters may show no change, or only a hyperæmia. On the other hand the kidneys are the seat of constant marked changes." He gave details of the lesions he had observed which were the same as those described by McDonald and by Thiemich. Practically the same experience was reported the next year by Rhonheimer[13]. Chown[14] reported one fatal case of pyelitis in which no microscopic lesion was demonstrated. The microscopic examination of the pelvis was not reported.

Finally,* to close the subject of autopsies, Helmholtz[15] reported that he had made serial sections of the pelves in cases of clinical pyelitis without being able to discover any inflammatory lesion.

In brief, then, we have complete information in only nine cases of "pyelitis" in infants of two years or less (7 : 10). In eight of these there was a suppurative nephritis with insignificant lesions elsewhere in the urinary tract, while in one there was a cystitis alone. The only case on record of pyelitis verified by microscopic examination is that reported by Cabot and Crabtree, and this report is incomplete. Two authors, without reporting their cases in detail, give as their conclusions that, in acute fatal cases of "pyelitis," the kidney uniformly is involved while the pelvis may or may not show lesions.

II. New Pathological Evidence.

The data here presented are taken from the records of the Departments of Pediatrics and Pathology at Johns Hopkins Hospital for the years 1911 to

* Drs. O. M. Schloss and J. R. Wilson have an article on the pathology of pyelitis in press (*Am. J. Dis. Child.*) at the present time. Their conclusions are similar to mine. I wish to express my appreciation of having been allowed the opportunity of going over their sections and protocols and of discussing the problem with them.

1924. Summaries of the clinical histories and pathological findings are given in all fatal cases of infants in whom the diagnosis of pyelitis, pyelonephritis, or pyelocystitis was made before death, on whom post mortem examinations were performed, or in whom the condition was first found at autopsy. The detailed reports of these cases are contained in the appendix.

The cases are divided into three groups.

Group 1 (*cases* 1-21) contains those that may be classed as acute or subacute. The striking features are (1) the uniform finding of multiple, focal, interstitial, suppurative lesions in the kidneys ; (2) the infrequency of any but the slightest pathological changes in the pelves, and their rarity in the ureters and bladder ; (3) the recovery of bacilli of the colon group in all cases where cultures were made (13 out of 21 cases) ; (4) the association with the infection elsewhere (12 of 21 cases) ; (5) the equal distribution between the two sexes ; and (6) the frequency of bilateral involvement, but with a tendency to more severe lesions on the right side (12 bilateral, 6 right sided, 2 left sided, 1 not known).

Group 2 (*cases* 22-25) shows four cases in which no lesion was found as a source of the pyuria.

Group 3 (*cases* 26-29) contains cases with chronic pyuria. These are perhaps the most interesting and instructive of all. Here with chronic pyuria and bacilluria accompanied by persistent marked symptoms or by a very slight general reaction, the pelves again show no source for the pus: while the kidneys are always involved and exhibit both acute, multiple, focal, suppurative lesions and inflammatory lesions in various stages of healing.

Case 30 is added to show that the condition may go on to complete histologic healing.

GROUP 1. *Acute or Subacute Cases.*

CASE 1. Boy of ten months, acutely ill for nineteen days in October, with symptoms simulating typhoid or meningitis. Pus and colon bacilli in urine. Head not examined at autopsy. Only lesion found was a bilateral, acute, focal and diffuse suppurative nephritis with pus draining from the tubules. No acute inflammation of the pelvis but a few mononuclear cells in the submucosa. Colon bacillus grown from the heart's blood, and a Gram-negative bacillus from the kidney.

CASE 2. Girl of ten months, taken ill in September and dying after one week of acute gastro-intestinal symptoms. Pathological lesion as in Case 1, and in addition a few leucocytes and small round cells in the pelvic mucosa. No bacteriological study. Head not examined at autopsy.

CASE 3. Boy of seven months, taken acutely ill in April with cough and fever. Course seven days. Urine contained albumen, pus, an occasional red blood cell and cast on the fourth day. Pathological lesions found at autopsy, small area of bronchopneumonia, bilateral renal lesions as in Case 1, and a few mononuclear cells in the pelvic and cystic submucosa. Colon bacillus grown from the urine and a staphylococcus from the blood during life.

CASE 4. Boy of ten months, taken ill in September with diarrhœa, sometimes bloody. No dysentery bacilli found in the stool, and no acute inflammatory intestinal lesion discovered at autopsy. Course nineteen days. Colon bacilli grown from the urine during life. Pathological findings; right-sided nephritis as in Case 1, a normal pelvis, a few large round cells and two small hæmorrhages in the submucosa of the bladder.

CASE 5. Girl of six months, taken acutely ill in June with gastro-intestinal symptoms. Course nineteen days. When first seen on the fifteenth day pyuria and colon bacilluria present. Post mortem findings, right sided nephritis as in Case 1 and a normal pelvis.

CASE 6. Boy of three months, ill for five weeks in the summer but with the acute phase lasting only about one week. Onset with "cold." Pyuria present at least two weeks. Renal lesions found at autopsy as in Case 1, with a few round cells in the pelvic submucosa and slight polymorphonuclear infiltration of the mucosa over the tip of one pyramid. Colon bacillus grown from the urine.

CASE 7. Girl of twenty-one months taken ill in July, with otitis media. Course thirty-five days, pyuria present at least two weeks. Terminal bronchopneumonia. Autopsy demonstrated a unilateral (left), suppurative nephritis, with focal and diffuse involvement. No demonstrable lesion in the pelvis, ureter or bladder.

CASE 8. Boy of six months, ill nineteen days in August. Onset with a "shaking chill," followed later by vomiting and loose stools. Pathological lesion found, bilateral nephritis as in Case 1, with slight round cell infiltration of the pelvic submucosa. No cultures.

CASE 9. Girl of thirteen months, ill for sixteen days in July. Clinical suggestion of otitis media but head not examined post mortem. Pyuria at least seven days. Renal pathological lesions as in Case 1, bilateral. Few mononuclear cells in the pelvic submucosa. No cultures.

CASE 10. Boy of six months ill twenty-two days in September. Onset with cough. Pyuria at least a week. Blood culture sterile. Colon bacilli grown from the urine before and after death, and from the kidney post mortem. Pathological lesion, the same bilateral suppurative nephritis with a few mononuclear cells in the pelvic submucosa.

CASE 11. Girl of six months, ill six weeks in January and February. Onset with blue spells; later cough. Otitis present at least three weeks, and pyuria at least same length of time. There was found, post mortem, pneumonia and pulmonary abscess, right sided suppurative nephritis as above described, and some mononuclear cells in the pelvic submucosa. No culture.

CASE 12. Boy of twenty-two months, taken ill in August. Course five weeks. Onset with vomiting and diarrhœa. Otorrhœa and pyuria at least two weeks. Colon bacilli grown from blood and urine. Pathological lesions found, enlarged kidneys with pus in collecting tubules, pelves normal.

CASE 13. Boy of two months, ill only two weeks. Onset with cough and fever. Terminal jaundice. Pus in urine on last day (only examination). Post mortem were found early bronchopneumonia, liver necrosias, bilateral suppurative nephritis, and a few mononuclear cells in the pelvic submucosa. Blood culture during life sterile. Post mortem cultures of liver, gall-bladder and spleen sterile. Culture of kidneys, colon bacilli.

CASE 14. Boy of four. Admitted for operation upon a chronic hydrocephalus. Not considered acutely ill. Few white blood cells in the urine. Died during operation. Pathological lesion, acute slight interstitial nephritis, pus draining from collecting tubules. Pelvis normal. I consider this an important case.

CASE 15. Girl of five months, taken ill in March with paroxysmal cough and high fever. First seen after one month of illness. Otitis media, doubtful pneumonia, marked distention of bladder, and pyuria then present. Died eight days later. At autopsy, bronchopneumonia, slight interstitial nephritis with masses of pus in the renal tubules, few mononuclear cells in pelvic submucosa.

CASE 16. Boy of four months, ill with cough for two weeks before admission. No diagnosis on admission; trace of albumen and occasional pus cell in urine. Rapid improvement then sudden relapse. Large number of pus cells in urine, and colon bacilli grown from it. Once more general improvement for two weeks, but pus and bacilli constantly in urine. No fever. Terminal acute diarrhœa for four days. Post mortem, right-sided acute suppurative nephritis with slight perivascular mononuclear infiltration of pelvic submucosa. Left kidney not examined microscopically.

CASE 17. Girl of six months, admitted in March. Otorrhœa for four months. Two weeks ago, pain on micturition. Fever for two weeks: diarrhœa two days. Convulsion on day of admission. Urine, much pus and Gram-negative bacilli, unidentified. Blood culture sterile.

Died on seventh day in hospital. At autopsy bilateral suppurative nephritis, injection of pelves, ureters and bladder, and many mononuclear cells in the pelvic submucosa.

Case 18. Boy of six months, admitted in September with an acute bacillary dysentery of one week's duration. Urine, some pus and an occasional red blood cell. On fifth day much pus. Died on seventh day. Pathological lesions, acute, ulcerative colitis; pus in collecting and convoluted tubules of left kidney. Macroscopic hæmorrhages in pelvic mucosa and submucosa but no pus cells.

Case 19. Girl of eight months. In hospital for six weeks for malnutrition; doing well; developed impetiginous lesions of skin, fever, then pyuria and colon bacilluria. These conditions persisted and she died three weeks from onset of illness. Otorrhœa for last three days of life. Autopsy findings :—ulcerative enteritis, cystitis, kinking of right ureter near bladder, exudate (?) in vesical opening of right ureter, dilatation of right ureter and pelvis to a slight degree, mild interstitial nephritis with pus cells in the renal tubules.

Case 20. Girl of thirteen months, taken ill in January. Course eight days, five from the onset of urinary symptoms. Streptococcus infection of middle ear and probably of blood stream. At autopsy acute, multiple, suppurative focal nephritis, slight infiltration of the pelvic and ureteral mucosa, very considerable infiltration of the submucosa of both these organs, together with some œdema and congestion. Colon bacilli grown from the kidney ; streptococci from the middle ear and heart's blood, while sections of the kidney showed Gram-positive cocci and Gram-negative bacilli. This was the only case that showed pelvic involvement sufficient in itself to have caused a moderate pyuria.

Case 21. Girl of four and a half months, taken ill in August with gastro-intestinal symptoms and dying at the end of ten days. The finding of old pleural adhesions suggested a previous infection, which was further borne out by the presence of proliferative changes in the kidney. Also present, an acute suppurative nephritis on the right side with a normal pelvis. Gram-negative bacilli in the tubules and glomeruli.

Group 2. (*No lesion found*).

Case 22. Boy of eight months, ill for eight days in September with acute colitis. Seen only on last day, at which time there was a marked pyuria. In the gross, yellow lines were seen running parallel to the striæ of the renal pyramids, but microscopically was found no abnormality beyond a few mononuclear cells in some Bowman's capsules. Pelves normal. The yellow lines were probably areas of suppurative nephritis, but this cannot be proved. No definite source of pus.

Case 23. Girl of two and a half months. Had never done well. Acutely ill eight days. Albuminuria, cylinduria and pyuria for at least four days. Primary pathological lesion, acute entero-colitis; subsidiary, acute bronchopneumonia and parenchymatous degeneration of the kidneys. No source found for the pyuria.

Case 24. Boy of two years. Said to have had pneumonia, convulsions and sore throat for three weeks before admission. On entrance to hospital only lesions were chronic otitis media and few leucocytes and casts in the urine. On the sixth day acutely ill. Suppression of urine. Next day albumen, casts and many pus cells. Death same day. At autopsy bronchopneumonia found. The kidneys, pelves, ureters and bladder were normal. No source of pyuria.

Case 25. Girl of three months. Ill for six weeks, first with nasal discharge and cough, then acute otitis media, and finally bronchopneumonia. Under observation for last three weeks. Kidneys became palpable while in hospital. Urine contained trace of albumen, few leucocytes, many epithelial cells and occasional cast. Colon bacilli grown from it three times. Blood culture sterile. At autopsy neither kidneys nor pelves showed source of pus. Small submucous hæmorrhage of bladder. Colon bacilli and streptococcus fæcalis grown from the kidney post mortem.

Group 3. *Chronic pyuria.*

Case 26. Girl of ten months, who had had a cough, and had done badly, for five months, and had had running ears for an indefinite time. On admission there were found a double otitis media, an empyema, and a urine loaded with pus and bacteria. The empyema (bacillus influenzæ,

Pfeiffer) was drained. Para-colon bacillus grown from urine. The child lived for two months, during which time the temperature was never above 100° F. The urine was repeatedly the same. Post mortem the kidneys in the gross were passed as merely congested, whereas microscopically, there were leucocytic infiltration along the medullary rays, collections of mononuclear and polymorphonuclear cells in the interstitial tissue of the cortex, irregularly depressed and compressed areas at the surface, and only slight mononuclear infiltration of the pelvic submucosa. The bladder was normal.

Case 27. Girl of seventeen months. Thirty-nine days before she was brought to the hospital this patient suffered from nausea, distention and occasional vomiting, together with fever that reached 104.5° F. These symptoms still persisted at the time of admission. The only pathological findings were in the urinary tract. The kidneys reached almost to the crests of the ilia. The bladder was up to the umbilicus. The urine contained albumen, large clumps of pus cells, hyaline and granular casts, and red blood cells. Colon bacilli grown from the urine. Death on the forty-eighth day of illness. At autopsy no lesion was discovered outside the urinary tract. The kidneys were enlarged, contained abscesses, and the capsule on being stripped off carried some bits of kidney tissue with it. The pelves were injected. Microscopically, there was found the usual acute suppurative nephritis, but in addition there were, both in the cortex and in the medulla, areas in the early stages of inflammatory repair. The pelves showed only slight submucous infiltration, as did the ureter and uretero-vesical junction. The bladder was normal.

Case 28. Boy of seven months, ill for an indefinite period. On admission both kidneys were palpable and the urine contained many pus cells and bacteria and a few red blood cells. Gram-negative bacillus grown from the urine. Death on the ninth day in hospital. Post mortem there was essentially the same picture as in Case 27.

Case 29. Girl of seven months, admitted in May on account of anuria and œdema of twenty-four hours' duration. Urine contained pus cells in clumps, red blood cells, casts and albumin. Colon bacilli grown from it. Afebrile for four days, then sudden flurry of fever for ten days with an increase in the pyuria. Thereafter well for one month except for an occasional leucocyte in the urine. Sent to a convalescent home, where during her five weeks stay she had several unexplained rises in temperature. Urine repeatedly normal. Finally there was a sudden attack of fever, accompanied by albumen, pus, and casts. She was re-admitted to hospital and died the same day. At autopsy the only gross lesions were two areas in the left kidney suggestive of early abscess formation. Microscopically there was suppurative interstitial nephritis with pus draining from the collecting tubules. In the sections available there was no evidence of any old lesion. The pelves were normal.

Case 30. A boy of fourteen months developed pyuria while under observation. The severe stage lasted for about two weeks, but there were a few pus cells in the urine for another two and a half months. Five months later he died of pneumonia, at which time there was no pus in the urine. At autopsy the kidneys did not show any scars of old lesions, nor was there any pathological change in the pelves.

III. Surgical Evidence.

The surgical evidence is very meagre, but goes to confirm the opinion formed from a pathological study. Jeffreys[9] reported the case of a girl of six months, admitted to the hospital with meningeal symptoms. Under observation the right kidney enlarged, followed by the left. The right subsided without interference, but the left continued to increase. Finally a left nephrotomy was done, with the release of a large quantity of purulent material. The surface of the kidney showed the mottled appearance, with necrotic areas, as described in the above autopsies. The baby made a good recovery. Watt[16] in 1923, reported the case of a girl of three and a half months suffering from a right-sided suppurative nephritis, who was cured by nephrectomy. There

was no dilatation of the pelvis, and apparently no obstruction. Unfortunately no bacteriological studies were made in either of the above cases.

In 1923 I was fortunate in observing a third case*, which occurred on the hospital service of Dr. L. Emmett Holt.

This was a girl of nine and a half months, who was taken ill on December 24th, 1922, with fever, listlessness, and vomiting. She was given castor oil and thereafter her stools were two or three a day. Her temperature ranged between 102° and 103°. She was very drowsy, and, from December 30, it was noted that she did not move her left arm. She was admitted to the Babies' Hospital on January 2. One's first impression was of an infant in the late stages of tuberculous meningitis. She lay in a semi-stuporous state, but was irritable on being disturbed; the head was turned to the right and retracted; the hands clenched, the arms held stiffly at the sides; the left arm was moved less than the right. There were fleeting flushes. The eyes did not follow a light. Nystagmus and internal strabismus were present. The left knee jerk was markedly exaggerated, and there was bilateral ankle clonus. Temperature 105.4°. Leucocytes 11,400, with 75% polymorphonuclears. The spinal fluid was normal. The only discoverable focus of infection was a pair of small, shallow ulcers of the soft palate, close to the anterior pillars of the fauces. The diagnosis was in doubt. By January 5th the leucocyte count had risen to 19,800. The next day the kidneys were first noted as palpable. The urine contained a moderate trace of albumen, a few epithelial cells, and an occasional leucocyte in the uncentrifuged specimen. For a week the condition progressed, with continually high fever, a mounting leucocyte count, which on January 11th reached 48,400, and with the further signs of kidney involvement of œdema, casts and microscopic hæmaturia. On the 13th, a cystoscope was passed by Dr. Bugbee. The bladder and ureteral orifices were normal. The right ureter was catheterized, about one half cubic centimeter of cloudy urine being obtained; and the pelvis was washed with boric acid, followed by silver nitrate. A Gram-negative bacillus was grown from this urine. Following this the temperature range was, 100° to 102°, and the leucocyte count dropped to 10,000, but the clinical picture remained the same. On January 24th a cystoscope was again passed. This time no urine was obtained from the right kidney until after washing with boric acid. B. coli communior was grown from the urine so obtained. Again there seemed little clinical improvement. The leucocyte count was now 7,600; the temperature curve ran along 100° to 102°, once reaching 104°. The urine still contained a few pus cells, epithelial cells, and an occasional cast. Finally, as a measure of desperation, operation was decided on. On February 3rd Dr. Bolling exposed the right kidney. It was found to be large, boggy, with several yellowish, depressed areas beneath the capsule. Two of these were explored but no pus found. The pelvis could not be felt to be enlarged. The capsule was split, and stripped from the anterior and lateral half of the kidney, and a hæmostat was passed through the body of the kidney towards the pelvis. There was no gush of urine. Drainage tubes were inserted. Four days later there was noted to be some clinical improvement. Ten days after the operation the temperature reached normal, and on March 10th the baby was discharged as well. The urine up to the time of discharge still contained a few pus cells.

All three of these cases showed kidney involvement associated with pyuria. Only one was studied bacteriologically, and in this B. coli alone was recovered from the urine. In the same case cystoscopy showed no bladder lesion, nor was there any great damming back of pus.

IV. Cystoscopic Evidence.

Jeffreys[9], in a series of eleven cases, included two little girls, one of 20 months and one 26 months, in both of whom the bladder was normal. Hinman[17]

* I wish to express my thanks to Dr. H. B. Wilcox for permission to report this case.

did not give the ages of his patients, so we cannot consider them here. Kretschmer and Helmholtz[18] in their series included three girls under two years of age. In all there was bilateral pyuria and bacilluria. No mention was made of the bladder, but Helmholtz elsewhere[15] says it was inflamed in all cases. Stevens[19] included one girl of 12 months in his series of 1921. As the bladder had been treated for some time before cystoscopy, the picture of inflammation found must be looked upon with doubt. In a later report[20] he included two cases in girls under one year. One was cystoscoped two weeks after the onset of fever. In the urine from the right kidney a few pus cells but no bacteria were found, from the left colon bacilli, while the bladder urine was sterile. In the second case, a chronic one, he found stricture of the urethra with trabeculation of the bladder, and bilateral bacilluria and pyuria. There was no inflammation of the bladder.

The evidence is somewhat conflicting, and too scanty to be of much value. It points to usual bilateral involvement of the upper urinary tract, with or without inflammation of the bladder. The criteria for the diagnosis of cystitis in these cases is not clear. Stevens' case of stricture of the urethra in a girl of less than one year is interesting and suggestive.

Discussion.

First let me again point out that this investigation has been limited to a study of pyuria in infants of two years or less. In reading the literature upon the subject of pyelitis in infancy, it is difficult to understand how the concept of primary inflammation of the renal pelvis arose, and how it came to be so generally accepted. But, once accepted, it has been "religiously adhered to as a fundamental axiom." I believe that the current conception of pyelitis is erroneous, leading to error in diagnosis, treatment and investigation. All the evidence available points to the kidney proper as the usual seat of the lesion in cases of pyuria in infancy.

Anyone basing conclusions on the nature of a disease upon dead-house pathology, is at once faced by the possibility that his results may be correct in the fatal cases, but that the pathology is not necessarily the same in the mild ones. While this may be so in the present instance, yet to argue in favour of a primary pyelitis as the pathological basis of mild cases is to speak for something which has never been shown to exist. As against the likelihood of a second type of lesion in the mild cases of pyuria I should draw attention to the following points. First, in the present series the deaths are not all due to the kidney disease (Cases 11, 14, 18 and possibly 15). Secondly, in Case 14 the disease was of so mild a nature that the child was not considered ill enough to contraindicate operation for a chronic hydrocephalus, yet as the only source of pyuria a minute area of suppurative nephritis was found. Thirdly, in the chronic cases are found old, healing lesions in the kidney side by side with recent, active areas of suppuration. If the pus had been originating in the pelves for the greater part of the time, and the renal involvement were a terminal event, one would expect to find some degree of pyelitis. There is none. And if

it were argued that with the onset of the renal inflammation the pelvic involvement has healed, one is then at a loss to explain the scars in the kidney.

Further work is necessary to settle the question, but so far it would appear that the common lesion in pyuria in infancy is a suppurative interstitial nephritis, with secondary involvement of the parenchyma. Whether there is a preliminary capillary damage due to toxins or organisms originating in a focus of infection elsewhere, or to vascular stasis or other causes, is not determined ; nor do we know if there is a heightened virulence of the associated colon bacilli ; nor yet what part obstruction to the urinary flow may play. The infecting organisms, having gained a foothold in the interstitial tissue, produce an acute inflammatory lesion, characterised by œdema, an outpouring of polymorphonuclear and, to a less extent, mononuclear cells, with degeneration of the neighbouring parenchymatous tissue and varying degrees of necrosis. Necrosis and liquefaction are, however, not prominent findings. The organisms and inflammatory products escape into the tubules, drain thence into the pelvis, and so appear in the urine. The pelvis is apparently very resistant to infection. That bacteria may be taken up here and passed back to the kidney by way of the lymphatics cannot be denied, but that such a thing occurs has not been proven beyond question. Certainly it is extremely rare for an acute inflammatory reaction to occur here, and that such reaction as is seen could be the source of a profuse pyuria seems impossible. It appears rather that in the mild cases the kidney drains and goes on to complete healing. In the more severe cases there are more extensive or more numerous lesions, with insufficient drainage. In the chronic cases there occur repeated infections of the kidney.

The gross appearance of the kidney in this disease varies according to the stage of the disease at which the patient dies. In the earliest cases the kidney, both externally and on section, may appear normal or slightly congested. The pelvis is normal. At a later stage the kidney is found swollen and congested. The degree of swelling is extremely variable, and may be scarcely noticeable, certainly not clinically appreciable. The outer surface usually shows many small, greyish white or yellowish white, flat or slightly depressed areas surrounded by a zone of hæmorrhage. The cut surface bears similar lesions both in the cortex and in the medulla, with some linear ones stretching through the pyramids. The pelvis is usually normal, though sometimes it has appeared congested or the seat of petechiæ. In the next stage abscesses are found in the substance and on the surface. Finally, in the chronic cases, there is a somewhat swollen kidney with a slightly adherent capsule, and with necrotic or suppurative foci as in the previous cases. There are certain cases which run their course without foci becoming visible to the naked eye. In these the kidney is usually swollen, soft and congested, and on section the surface is greyish and slimy.

There can be no doubt that a second type of primary lesion as a source of pyuria occurs, though in this series it has been infrequent. This is an acute glomerulitis, such as was described by Bell and Hartzell[21]. It is possible that a certain number of cases looked upon as primarily interstitial might, upon

further examination, prove to be glomerular, but the gross appearance of the two types is entirely different.

2. With a second prevalent belief relative to "pyelitis" it is impossible to agree; namely, that the disease affects, almost exclusively, female babies. In the early work upon the subject it seems that no attempt was made to be sure that the urine, upon which the diagnosis was based, was uncontaminated. Overlooking the great possibility of such contamination in girls, all cases of pyuria were looked upon as cases of inflammation of the urinary tract, and so there arose the idea of the almost exclusive occurrence of the disease in girls. The error is repeated even up to the present time. There are three main sources of error here. First, and probably most common, is that due to catarrhal vaginitis, itself secondary to some acute febrile condition such as tonsillitis, pneumonia, appendicitis or one of the exanthemata. Second is specific vaginitis, which is frequently associated with urethritis. Third is contamination from the stool in the acute enteritides. Unless all these sources are ruled out, no case can be considered as one of true pyuria, and I know of no large series of cases in which this has been done. It cannot then be said, on the evidence at hand, that the disease is one predominantly affecting one sex.

The idea has become so firmly fixed, however, and is so universally held, that it has of itself led to still further error. If a girl runs a temperature, which is not at once explainable, urinalysis is done in the expectation of finding pus, and so the incidence among girls increases. But on the other hand it is considered so rare in boys, that, in the same circumstances, urinalysis is frequently omitted, and the incidence among boys accordingly decreases.

In the period under consideration there occurred in Harriet Lane Home 105 cases of pyuria under two years of age. Of these 73 were in girls and 32 in boys. Allowing for the above factors of error we are still left with the probability of a predominance in girls. The mortality figures are probably nearer to the true sex distribution, 60% girls and 40% boys, but for the present it must be admitted that accurate figures are not available.

Sex must then be considered as a probable ætiological factor, and plays its part in all likelihood, by offering an additional route of infection in girls. It seems very doubtful if infection can ascend through the urethra in male infants. Further, the pathological picture presented in both sexes is usually a definitely interstitial one, suggesting a blood stream infection. In the absence of positive proof it seems reasonable to believe that the route is by way of the blood stream in boys, and in a similar number of cases in girls. In the remaining bilateral cases in girls the assumption of an ascending infection by way of the urethra appears justifiable, and certainly some of the cases of cystitis uncomplicated by a lesion higher in the urinary tract probably originate in this way.

3. To explain the more frequent occurrence of right-sided lesions, the theory of direct lymphatic extension from the cæcum has been invoked[22] by Franke. So far as I am aware his original investigations have never been confirmed. In point of fact, in infancy, the left kidney is much more closely connected to the colon than is the right. Very frequently only the lower pole of the right

kidney is in contact with the large intestine, or there may be no connection whatever. The lower half of the kidney is not more frequently involved in the disease than is the upper. Further the pelvis itself is rarely in direct relation with the colon. There is, however, a difference between the anatomical relationships of the two kidneys, which may be of importance. The right is overlapped by the liver, which may even reach down and cover the pelvis and renal vessels. In the course of acute infections it is a common occurrence to find the liver greatly enlarged. With the infant lying flat on its back this might well bring pressure to bear on the right kidney with some consequent stasis and lowering of resistance. Helmholtz and Field[23] have recently demonstrated that complete occlusion of the renal vein for as short a time as three minutes so alters the kidney permeability as to permit bacteria to pass through in a very short space of time. The liver further keeps the right kidney at a lower level than the left. Whether this is due to the kidney being pushed down or prevented from rising up during fœtal life I am not sure, but in either case this would offer a greater opportunity for ureteral kinking on the right. In a small series of cases I have observed multiple, small kinks of the first part of the ureter in young infants. I cannot say that they have been more often right sided, nor have they been, as a rule, associated with any disease of the kidney. Whether they have any significance is uncertain.

4. Upon two other ætiological factors the present study throws some light. The first is the bacterial agent involved. In all cases reported here in which a bacteriological study was made a bacillus of the colon group was found. The significance of this cannot be determined at present. We do not know if it was the sole bacterium, or if it was only a secondary invader. In one case a Gram-positive coccus was found in the kidney sections in association with Gram-negative bacilli, while only B. coli was grown from the urine. While it is possible that on culture B. coli might overgrow other pathogenic organisms, yet to believe that it would do so uniformly is asking a good deal. The assumption that this occurs is not justifiable until further proof is forthcoming. It is also possible that the kidney successfully overcomes some primary invader, only to lay itself open to a later attack. The fact that Thiemich[19] did not study his cases bacteriologically has been held to vitiate his conclusions, and the finding of abscesses in the cortex in his cases has been adduced as evidence of infection by one of the coccus group. Our present study goes to confirm Thiemich's belief.

The second apparent ætiological factor to which attention is called is that of infection elsewhere. This has been repeatedly observed by other authors. In this series parenteral infections have been somewhat more frequent than enteral, nor have the kidney lesions in the latter cases been particularly severe. Studying the seasonal incidence in the larger group of all cases occurring in the hospital it is found that there are two distinct maxima, one in February and March, and a much higher one in August and September. These correspond with the periods of respiratory infection and of intestinal disturbance.

5. Finally attention is drawn to certain appearances which have led to incorrect diagnoses of inflammation of the urinary tract. The mucosa of the bladder, ureters and pelves is shed very rapidly after death. We have seen the ureter so filled with desquamated epithelium that it appeared as though blocked with exudate, and we have repeatedly examined turbid urine from the pelves, believing that we were dealing with cases of pyelitis, only to find that the turbidity was due to epithelial cells.

Macroscopically this desquamation may lead to the erroneous diagnosis of catarrhal inflammation. Another error is that of taking the deep red discoloration of the urethra, which occurs post mortem, for evidence of inflammation. Macroscopic diagnosis of inflammation of the urinary tract mucosa after death is of little value.

The question has often been asked " What is the relation between pyelitis of infancy and pyelitis of pregnancy ? " Might we not better inquire " What is the relation of the pyurias of infancy to the nephritis of later life ? "

Conclusions.

1. The term " pyelitis of infancy " is a misnomer.

2. The microscopic lesions found in this investigation agree with those found by previous observers.

3. The common lesion is a multiple, focal, suppurative, interstitial nephritis, with which is associated occasionally some degree of pyelitis, and rarely cystitis.

4. The lesion is usually bilateral, but when it is unilateral it is more often right-sided than left-sided.

5. Rarely the lesion found is an acute glomerulitis, or a cystitis.

6. Pyelitis as a sole lesion seldom, if ever, occurs.

7. The lesions described are probably more frequent in girls than in boys.

8. The commonly associated bacterium is probably the Bacillus coli.

9. The renal lesions are usually secondary to an inflammatory process elsewhere.

I wish to express my thanks to Dr. John Howland and to Dr. W. G. MacCallum for placing their departmental records at my disposal for the purpose of this study.

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APPENDIX.

Cases in Detail.

Group I.

Case 1. Boy, 10 months, admitted in October. Five days ago, feverish. Next day, hands shook. Third day, vomited, and bowels moved only with castor oil. Fourth and fifth days, attacks in which feet trembled, hands clenched, eyes rolled up, and he tended to throw head to right. Temperature 101° to 104°. Appetite good to fourth day. Water freely taken. In hospital: knees drawn up, arms thrown over face, continual tremors, irritability, impression of great pain. Neck not rigid, knee jerks hyperactive, bilateral Babinski's sign. No other localizing signs. Temperature 103.2°. W.B.C. 37,000; polymorphs 73%. Spinal fluid normal. Urine, pus and colon bacilli. He passed from irritability to drowsiness, and finally stupor. Urine repeatedly the same. W.B.C. 26,000 to 40,000. Ninth day in hospital, refusing food. Twelfth œdema. Fourteenth, phthalein a trace. Death. *Autopsy.* Head not examined. Lungs and intestines normal. Kidneys: right, 125 grams, very soft. Capsule strips easily. Surface nodular due to pin-head size, yellowish white areas, standing out from redder kidney substance; small hæmorrhages. On section various portions blurred, and in cortex and medulla small yellowish areas and hæmorrhages. Pelvis filled with a cloudy material, but on scraping it away mucosa smooth and glistening. No injection and no hæmorrhage here or in ureter. Left, 65 grams, but similar appearance. Also one soft pale yellow, raised area, 1×2 cm., wedge shaped on section, its centre fluid. *Microscopic.* Pale areas of œdematous tissue with widely spaced tubules and no cellular infiltration alternate with darker areas made up of polymorphonuclear cells and hæmorrhage and a few tubules with degenerated epithelium. Lumen of tubules stuffed with polymorphonuclear cells and a few mononuclear and red blood cells. Hyaline changes in glomeruli and some red cells in the capsular space. In the medulla, general polymorphonuclear infiltration and tubules dilated with pus. Pelvic mucosa ragged but no signs of acute inflammation; in submucosa groups of mononuclear cells. Ureter and bladder normal.

Case 2. Girl, 10 months, admitted September. "Born with a cold," For one week vomiting and diarrhœa. Died one hour after admission. *Autopsy.* Head not examined. Intestines, some "cloudy swelling and round cell infiltration." Kidneys together 50 grams; petechiæ. Irregular yellowish patches of same consistency as intervening renal tissue scattered over surface. On section yellowish areas and hæmorrhages extend from outer margin of cortex along tubules into pyramids. Pelves slightly congested. In ureters clumps of white material. Bladder congested and roughened. *Microscopic.* Interstitial tissue of cortex in part normal; again slight polymorphonuclear infiltration; in other areas dense collections of these cells surrounded by zones of congestion. No leucocytes in glomeruli; a few in some convoluted tubules; masses of pus in collecting tubules. In pelvic mucosa an occasional leucocyte or small round cell. Submucosa, mild infiltration with mononuclear cells, especially about blood vessels. Bladder submucosa slightly congested.

Case 3. Boy, 7 months, admitted in April. Four days ago cough and high fever. On admission general appearance suggested acute meningitis. Pharynx red; abdomen markedly distended; temperature 103°; urine, marked trace of albumen, many pus cells, occasional red blood cells and granular casts. Spinal fluid normal. Third day, urine alkaline, phthalein 15%. Fifth day a staphylococcus (type not stated) grown from blood, B. coli from urine. Urine on this day, albumen, no pus. Died same day. Temperature always above 101°, usually over 102°, and had reached 104°. *Autopsy.* Head not examined. Small area of bronchopneumonia. Intestines normal. Kidneys: soft, capsule strips easily; surface pale yellow with numerous small, poorly defined areas of a more pronounced yellowish colour, a few pale grey areas, and a few minute hæmorrhages are scattered it. Cut surface pale; numerous poorly defined streaks running parallel to striæ of cortex and pyramids, no definite abscesses. Turbid fluid in pelvis; several petechiæ in mucosa. Bladder and urethra normal. *Microscopic.* In interstitial tissue larger and smaller clumps of inflammatory cells. Glomeruli, no infiltration. Pus and red blood cells in many tubules. Pelvic mucosa poorly preserved but no infiltration. In submucosa possibly some mononuclear increase. Bladder similar.

Case 4. Boy, 10 months, admitted in September. Two weeks, loose stools; three days, blood in stools. No vomiting. Appetite poor. On admission no significant clinical signs. Urine, trace of albumen, marked acetone, and pus. T. 101°. W.B.C. 11,600. Stool, no dysentery bacilli. Temperature increased from day to day, fluctuating widely. Stools, blood. Urine on second day, and daily thereafter, pus, hyaline, granular, and cell casts. B. coli grown from urine. Third day, phthalein 47%. Died fifth day, after a series of convulsions. *Autopsy.* Head not examined. Intestines, few petechiæ, and some swelling of lymphoid tissue. Right kidney, 39 grams. Capsule strips readily. In middle of lateral border two areas about 7 mm. in diameter dark red in colour, and containing several yellowish spots; wedge shaped on section, extending to pyramids. Renal detail blurred. Pelvis granular and slightly injected. Ureters normal. Left kidney: 40 grams.; no gross foci, otherwise kidney and pelvis like right. *Microscopic.* Left kidney; cloudy swelling. Right kidney: cloudy swelling and congestion, many minute collections of leucocytes in interstitial tissue, with necrosis of neighbouring tubules; one large area of polymorphonuclear infiltration and necrosis in medulla and one in cortex; collecting tubules stuffed with pus; pelvic mucosa normal, and submucosa slightly congested. Bladder mucosa somewhat shredded; in submucosa, a few large round cells, and two small hæmorrhages.

Case 5. Girl, 6 months. Onset in June. First day, restless, irritable, vomited three times. Next day, high fever. Thereafter anorexia and diarrhœa. Admitted fifteenth day, very ill. Neck slightly rigid; abdomen distended; liver easily palpable; in right iliac and lumbar region a firm, immovable, apparently painless mass. Urine, much pus, no casts. B. coli grown from it. W. B. C. 45,000; 85% polymorphonuclears. Blood culture sterile. Spinal fluid normal. Diarrhœa and distension persisted. Temperature 100° to 105°. Fourth day, comatose, at times convulsive; death. *Autopsy.* Head not examined. Only lesions in urinary tract. Right kidney: 80 grams; numerous irregular, yellowish areas on external and cut surface. Pelvic mucosa pale, no injection. Left kidney, 75 grams; mottled; vessels at base of pyramids injected. Pelvis normal. *Microscopic.* Right kidney: interstitial tissue generally infiltrated

with polymorphonuclear cells ; abscesses in cortex ; epithelial necrosis. Pelvis not shown. Left kidney : œdema ; pink-staining substance in tubules ; glomeruli, pelvic mucosa and submucosa normal. Bladder mucosa and muscularis normal ; slight perivascular infiltration of submucosa.

Case 6. Boy, three months, admitted in November. Three weeks ago, spell in which held breath and turned blue, but not rigid. Week later, similar spell ; arms stiffly flexed and head retracted. Past two weeks, attacks as often as eight a day. Past week, a cold, and six days, a rash. Appetite good, stools normal. On admission not acutely ill ; dry, scaly skin with some pustules ; general glandular enlargement ; T. 97° ; W.B.C. 12,400. Urine, trace of albumen, few leucocytes. Wassermann negative. Erb's sign negative. Attacks were "like the breath holding spells of older children." For four days temperature normal. Fourth day : urine, many epithelial cells, few leucocytes. Refused food, vomited. Seventh day, temperature 102.5°, the highest point while in hospital. Urine, albumen, clumps of pus cells. Phthalein 20%. Temperature slowly fell, but condition became worse. Diarrhœa and vomiting developed. Tenth day : urine, marked albumen, many hyaline and granular casts, many pus cells. Died on twelfth day. *Autopsy.* Head not examined. Lungs and intestines normal. Right kidney : 11 grams ; capsule strips with ease ; on external and cut surface numerous circumscribed and confluent, opaque white areas, no hæmorrhages. Pelvic mucosa delicate, pale grey, glistening. Ureter normal. Left kidney, same as right. Bladder and urethra normal. *Microscopic.* At periphery of cortex, wedge shaped areas of polymorphonuclear infiltration alternating with relatively normal tissue. Glomeruli swollen but no infiltration. Tubular degeneration. Many convoluted and collecting tubules filled with pus. Interstitial tissue of medulla much less involved than cortex. Mucosa of pelvis normal ; in submucosa a few round cells. Slight polymorphonuclear infiltration of mucosa over tip of one pyramid. Ureteral mucosa normal ; muscularis congested ; in submucosa a few polymorphonuclears. Urine culture :—B. coli communis.

Case 7. Girl, 21 months, admitted in July. July 1st acute otitis media, retention of urine, pain on micturition ; urine negative. Seen in dispensary July 17 ; refusing food, feverish, irritable. Admitted July 23 : injected pharynx, dull ear drums, pus and albumen in urine, T. 105°, W.B.C. 26,000. Thereafter temperature 100° to 105°, more often above than below 103°. July 29 : phthalein 30% ; blood culture sterile ; cough. August 2 ; urine, pus and few casts. August 4 : ear drums ruptured ; Widal negative; child restless and twitching; œdema of ankles and eyelids. Next day, abdomen distended ; convulsions ; death. *Autopsy.* Head not opened. Small area of lobular pneumonia. Intestines normal. Right kidney : 70 grams ; externally and on section normal. Left kidney 105 grams ; abnormally firm ; abscesses on surface ; on section, an area near anterior pole where grey lines extend through medulla and cortex to end in a conglomerate abscess. Mucosa of pelvis congested. Ureter, no obstruction. *Microscopic.* Interstitial tissue variously involved ; in cortex general infiltration and in two places, necrosis ; in medulla, œdema, moderate infiltration, congestion with hæmorrhage. Glomeruli normal, except in necrotic areas. Convoluted and straight tubules degenerated, and contain pus cells, small and large round cells, and casts. In one pyramid, an extensive localized area of infiltration, none towards tip. Pelvis normal. Epithelium of ureter desquamated, and a minute area of small cell infiltration at one point. Bladder normal.

Case 8. Boy, 6 months, admitted in August. Fifteen days ago, "shaking chill," followed by high fever. Similar chill next day. "Feverish" two or three days. Bowels became loose tenth to fifteenth day, thirteenth to fifteenth blood in stool. On admission critically ill ; buttocks severely excoriated ; T. 101° ; W.B.C. 52,700; urine, marked albumen, few casts, many pus cells. No dysentery bacilli in stool culture. Following day, T. 100° to 100.9° ; W.B.C. 48,800 ; Urine, same. Fourth day, convulsions and death. *Autopsy.* Head not examined. Beginning bronchopneumonia. Intestines normal. Fascia surrounding kidneys œdematous. Kidneys together 65 grams. Capsules strip easily. Kidneys studded with creamy coloured areas, irregular in size and contour, chiefly in cortex. Pelvis congested, and filled with cloudy fluid containing cream coloured flecks. Ureters normal. *Microscopic.* In cortex alternating areas of polymorphonuclear infiltration destroying tubules and glomeruli alike, and of cloudy swelling without infiltration. Some glomeruli in latter areas more cellular than normal. Many collecting tubules filled with pus. Epithelium over pyramids, and that lining pelvis intact. Slight round cell infiltration of pelvic submucosa, and of deep muscular layer of bladder.

CASE 9. Girl, 13 months, admitted in July. Nine days ago, restless. Next day refused part of food, and vomited. Fourth day, temperature 104° ; range thereafter 98.6—104°. Two stools a day ; no more vomiting ; at times quite distended ; no pain on voiding. Eighth day, chill or convulsion. On admission : T. 104° ; pale, irritable, hyperæsthetic ; right ear drum slightly reddened ; urine, pus no casts ; W.B.C. 28,000. Refused food and water, was nauseated and frequently vomited. Fourth day temperature normal ; other symptoms continued. Died on seventh day. *Autopsy.* Head not examined. Congestion and lymphoid hyperplasia of intestines. Kidneys together 100 grams ; deep red, with irregular, yellowish areas scattered over surface, on section fine yellow streaks lead from these areas towards deep red bases of pyramids ; tips of latter pale. Ureters and pelves normal. *Microscopic.* In cortex, areas of dense polymorphonuclear infiltration and hæmorrhage, and some actual abscess formation with necrosis. Pus in many tubules. Pelvic mucosa normal ; groups of mononuclear cells in submucosa.

CASE 10. Boy, 10 months, admitted in August. For two weeks, cough and fever, stools green, no vomiting. On admission : no localizing pathological signs ; T. 100° ; W.B.C. 40,000 ; urine, trace of albumen, few granular casts, large quantity of pus, culture B. coli ; spinal fluid normal ; blood culture sterile. Loose stools and pyrexia continued. Temperature not above 101.5. Terminal bronchopneumonia. Died on eighth day. *Autopsy.* Head not examined. Intestines normal. Right kidney, 45 grams ; capsule strips easily; foci on surface, in cortex and less in pyramids ; yellow lines running through latter. In pelvis few c.c. turbid fluid ; mucosa congested. Ureter not distended ; mucosa congested. Left kidney 40 grams, resembles right, Bladder normal. No urethral obstruction. *Microscopic.* Large abscesses not seen. In many tubules debris, large round cells and polymorphonuclears. Patchy infiltration of interstitial tissue with leucocytes and round cells. Similar cells in pelvis but mucosa normal. Small perivascular collections of round cells in peripelvic tissue. Slight congestion of ureter and bladder. *Bacteriological* ; heart's blood sterile ; kidney, B. coli communior ; urine, B. coli communior.

CASE 11. Girl, 6 months, admitted in January. Three weeks ago cried out during night, rolled head from side to side, and stiffened out. Four similar turns in first twenty-four hours, after which she seemed well. Week later blue spells during which she felt cold. For four days before admission, high fever, cough, green stools. On admission attack similar to those at onset ; T. 104° ; neck stiff ; urine, much pus ; otitis media. Repeated spells of cyanosis. Died in about two weeks. Terminal pneumonia. *Autopsy.* Head not examined. Bronchopneumonia and lung abscess present. Intestines normal. Kidneys, twelve grams each. Left kidney, pelvis, and ureter normal. Right kidney : capsule slightly adherent ; surface mottled grey and red, and similar patches in cortex and medulla ; pelvic mucosa smooth, but a few hæmorrhagic flecks present. Right ureter somewhat dilated near the bladder, mucosa pale and smooth. Bladder moderately distended ; mucosa normal. *Microscopic.* Left kidney, no definite lesion. Right kidney ; capsule normal ; interstitial tissue patchy, mononuclear and polymorphonuclear cellular increase ; masses of these cells in some tubules ; pelvic mucosa normal ; ome mononuclear cells in submucosa, and more in peripelvic fat, mainly perivascular.

CASE 12. Boy, 22 months, admitted in August. Three weeks ago acute vomiting and diarrhœa. Vomiting stopped, but diarrhœa continued. Not "feverish." On admission : dehydration ; otorrhœa ; indefinite signs in chest ; T. 102° ; W.B.C. 12,800 ; urine, pus. Right kidney became palpable under observation. B. coli grown from blood and from urine. Temperature range, first week 98.6° to 102°, second 102° to 105°. Death on sixteenth day. *Autopsy.* Record of organs other than urinary tract mislaid. Temperature curve suggested a pneumonia. Kidneys together 100 grams. Urinary tract normal throughout. *Microscopic.* Glomeruli normal. Few areas of infiltration interstitial tissue. Cloudy swelling. Clump of pus cells in tubules. Pelvic mucosa and submucosa normal. Bladder normal.

CASE 13. Boy, age 2 months. For two weeks cough and fever. Two days ago, jaundice appeared and same day had a convulsion. On admission only definite findings pyuria and jaundice. Blood culture sterile. *Autopsy.* Head not examined. Beginning bronchopneumonia. Liver necrosis. Kidneys : 60 grams each ; capsule removed with ease ; surface smooth, and interspersed with small, round, greyish areas. On section : cortex swollen ; striations regular ;

small greyish points scattered through cortex, and extend as streaks into the pyramids as far as calyx. Pelvis normal. *Microscopic.* Capsule uninvolved. Interstitial tissue œdematous, and infiltrated with inflammatory cells. Masses of pus in distended tubules from periphery to pelvis, more marked at periphery. Pelvic mucosa normal, round cell infiltration of submucosa at angles of reflection. Bladder mucosa and muscularis normal. Few small groups of large round cells in submucosa. *Bacteriology*: liver, gall-bladder, and spleen, sterile; kidneys, B. coli.

Case 14. Boy of four. Admitted for operation on a chronic hydrocephalus. Temperature 101°: few pus cells in urine; not considered acutely ill. Died during operation. *Autopsy.* Kidneys normal. *Microscopic.* Minute area of polymorphonuclear infiltration of interstitial tissue; pus draining from collecting tubules; pelvis normal.

Case 15. Girl 5 months, onset in March. One month ago paroxysmal cough, frequently followed by vomiting; high fever; listlessness and apathy. After six days vomiting stopped, other symptoms continued. In hospital: right ear drum red and bulging; pharynx congested; râles over right lung; liver, spleen and kidneys palpable; bladder to umbilicus, and urine could be expressed. Urine pus only. W.B.C. 32,000. Sixth day respirations more rapid, and temperature higher. Eighth day, death. *Autopsy.* Head not examined. Moderate bronchopneumonia. Intestines normal. Kidneys: 50 grams each; capsule strips easily; external surface smooth, glistening, greyish red; cut surface, dull, pasty, greyish red, with yellowish points throughout cortex and fine lines through pyramids; few petechiæ. Pelvis not dilated, but mucosa injected, and few petechiæ. Ureters same. Bladder distended, and mucosa congested. *Microscopic.* Glomeruli congested; some unduly cellular; occasionally one or two large mononuclear cells free in the capsular space. Some tubules collapsed; others slightly dilated by granular pink substance; others contained pus. A few small hæmorrhages. Most of pelvic mucosa shed off; remaining part normal. In submucosa a few large mononuclear cells. Similar condition in beginning of ureter. Bladder normal.

Case 16. Boy, 4 months, admitted in May. Cough for two weeks. For two days loose stools, vomiting and listlessness. In hospital, irritable, but no localizing signs; T. 98.6°; W.B.C. 16,000; urine, trace of albumen, occasional pus cell. Rallied quickly, and for three days appetite good, stools improved, and temperature only once above normal. Fourth to seventh day, apathetic, and uttered shrill cries; T. 100.5° to 101.5°; urine, pus. Blood culture sterile; urine, B. coli. Seventh to twenty-second day in hospital temperature normal, general condition improved, urine always loaded with pus, and B. coli grown from it. Phthalein 45 to 50 per cent. On twenty-second day fever and frequent stools, and in four days he was dead. *Autopsy.* Head not examined. Lungs and intestines normal. Left kidney; 22 grams; normal. Right 20 grams; on section a small amount of slimy fluid oozes out; many small yellow flecks scattered here and there. *Microscopic.* Right kidney only examined. In some sections generalized infiltration with mononuclear and polymorphonuclear cells, with a pink staining hyaline material in some glomeruli and tubules, and clumps of cells in others. In other sections focal accumulations of cells, mainly mononuclear in type, and submucous infiltration with similar cells at the tip of a papilla. Pelvic mucosa normal with slight perivascular infiltration of submucosa.

Case 17. Girl 6 months, admitted in March. At two months, dermatitis, furunculosis, and otitis, and thereafter otorrhea off and on. Two weeks ago cried when voided, and was feverish. Fever continued. Two days ago, diarrhœa. Next day temperature higher. On day of admission convulsive attack. On admission T. 103.6°, and that night rose to 105°; ear drums slightly injected; abdomen distended; W.B.C. 29,000; urine, pus only. Gram-negative bacillus grown from the urine. Blood culture twice sterile. Phthalein 24% on day of admission, 16% on sixth day. Death on seventh day, preceded by convulsions and abdominal distention. *Autopsy.* Head not examined. Small areas of bronchopneumonia. Kidneys: 70 grams each; not so firm as usual; capsule strips easily; surface smooth and mottled with areas of brown and yellow; striæ distorted by small yellow zones. Pelves and ureters mildly injected, but no exudate. Bladder injected, and a few hæmorrhages. *Microscopic.* Interstitial tissue extensively infiltrated, mainly with round cells, relatively few polymorphonuclears. Many glomeruli and tubules destroyed by this infiltration; in other tubules, masses of these cells. Pelvic mucosa ragged, many mononuclear cells in submucosa. Ureter same. Bladder, submucous congestion.

CASE 18. Boy six months, admitted in September. Bloody diarrhœa, and vomiting for one week. On admission acute bacillary dysentery,and bilateral otitis media; T. 100.5°; W.B.C. 9,300; urine, two or three pus cells per high power field, and occasional red cell. Fifth day: urine, many pus cells and few red cells. Died on seventh day. *Autopsy.* Ulcerative colitis present. Kidneys together 35 grams; normal externally and on section. Right pelvis normal; left of normal size, but filled with 1 c.c. of thin, grey fluid. Mucosa dull, congested, and, particularly about the tips of the pyramids, infiltrated with petechiæ. Left ureter normal in size; mucosa dull, and few petechiæ. Bladder and urethra normal. *Microscopic.* Right kidney, cloudy swelling. Left: interstitial tissue congested; convoluted tubules degenerated, clumps of cells, mostly polymorphonuclears, in a few; more pus in collecting tubules. Pelvis, no inflammatory cells, but submucous hæmorrhage.

CASE 19. Girl 8 months, admitted in August. After six weeks treatment in hospital for malnutrition began to run irregular fever, reaching 103.4° on third day. On same day impetiginoid skin lesions first noticed. W.B.C. 26,000. Urine, heavy sediment of pus. B. coli grown from urine. Temperature from now on irregularly elevated rarely above 101°, never over 103°. Three days before death right otorrhea. Died three weeks from onset of fever. *Autopsy.* Head not examined. Ulcerative enteritis present. Kidneys externally and on section normal. Right pelvis slightly larger than normal, injected and contains small amount of cloudy material. Right ureter dilated to about size of lead pencil, and injected. Small plug of exudate (?) in uretero-vesical opening. Lower end of ureter, 2 cm. from bladder, sharply kinked, but dilated below this. Left pelvis and ureter normal. Bladder mucosa injected, and trigone covered by diphtheritic exudate. No urethral obstruction. *Microscopic.* Small collections of polymorphonuclear cells in interstitial tissue, some encroaching upon tubules. Few polymorphonuclear leucocytes in some collecting tubules. Glomeruli congested. No sections of pelvis ureters, or bladder available for study.

CASE 20. Girl, 13 months admitted in January. Eight days ago a little fever, and slight regurgitation. In a day or two, screamed in sleep as though in pain; ear drums said to be normal; few pus cells and blood cells in urine. Fifth day, ear drums inflamed; some cough; a good deal of discomfort; fever continued. Next day ear-drums incised without benefit to patient; T. 104°; stuporous. Lumbar puncture attempted at home without success. Admitted eighth day and died in a few hours, while optochin was being injected intraspinally. Right otorrhea; left drum opened with liberation of pus. W.B.C. 20,000. Urine not obtained. *Autopsy.* No meningitis, but a recent intracranial hæmorrhage, possibly due to first lumbar puncture. Lungs and intestines normal. Kidneys: right 65 grams, left 60; capsule strips easily; about thirty, yellowish white, slightly raised, roughly circular, necrotic looking areas of various size, but averaging about 2 mm. in diameter both over surface and on section. Ureters dilated, and deep red. Bladder normal. *Microscopic.* Complete cross sections of kidney with pelvis and piece of ureter obtained. Under hand lens there was seen in ureter and less marked in pelvis a dark line deep to mucosa about 0.2 mm. wide. In cortex were five areas of a similar dark colour, two circular, with lines running to surface, and three wedge shaped with base at surface.

With higher magnifications ureter was seen to contain some exudate, both cellular and structureless, together with Gram-negative bacilli and gram-positive diplococci. Cells mostly polymorphonuclears, with a scattering of large and small mononuclears. Mucosal surface intact save at one point near pelvis, where there was a small area of disintegration, probably a post mortem change. In substance of mucosa were a few leucocytes and round cells. Submucosa and muscularis œdematous, and infiltrated with mononuclear cells and a few leucocytes. These cells, tending toward linear distribution in deep submucosa, formed the dark line seen under the hand lens. Occasionally they were grouped about a blood vessel, the vessels themselves being very congested.

Passing to the pelvis the œdema lessened. The cellular zone approached nearer the surface, in places was extremely dense, and proportion of polymorphonuclear cells in it increased. For the most part the pelvic mucosa showed very slight infiltration with leucocytes. Over the tip of a pyramid most of the mucosa was gone, while here and there were leucocytes adhering to the surface so exposed. It was impossible to say whether this was an artefact or not, but it did not suggest it very strongly. Close by was an area of marked infiltration of the mucosa.

In kidney, a good deal of infiltration at points where large blood vessels entered. In the papillæ the interstitial tissue at the very tip showed a few infiltrating cells ; most tubules empty ; occasional one filled with exudate and a few bacteria. About 2 mm. from this comparatively free tip all was chaos. An occasional tubule could still be seen, but for the most part the picture was one of necrosis and hæmorrhage. Throughout medulla generally there was interstitial infiltration, with here and there sharply marked off foci. In cortex, degeneration of epithelium and granular exudate in tubules and in some glomeruli, with here and there fairly well localized, large and small abscesses surrounded by hæmorrhage. Predominant cell polymorphonuclear. *Bacteriology.* Right ear culture :—Streptococcus hæmolyticus. Heart's blood culture :—Streptococcus hæmolyticus. Ureter culture :—B. coli communis. Ureter smear :—Few Gram-positive and Gram-negative bacilli.

Case 21. Girl, 4½ months, admitted in August. August 1st, acutely ill with fever, vomiting and diarrhœa. Admitted on the fifth, and died five days later. Continuous fever ; at times 105°. Voided well, but no urinalysis report available. *Autopsy.* Head not examined. Old pleural adhesions and a beginning fibrino-purulent peritonitis (probably simply a sterile reaction). Kidneys : right 32 grams ; swollen and grey ; raised areas, each about 2 mm. in diameter on surface, surrounded by and infiltrated with hæmorrhage. On section these descend into cortex to medulla, which is streaked with yellowish lines. Pelvis injected and pyramids hæmorrhagic. Left 23 grams, firmer, and red ; normal on section. Bladder normal. *Microscopic.* Right : small subcapsular hæmorrhage. Œdema of the interstitial tissue with beginning proliferation. In a few glomeruli increased cullularity of tuft, or capsular space contained a few round cells or leucocytes. Still less commonly, slight proliferation of Bowman's capsule. Near periphery many tubules choked with leucocytes, red blood cells, and mononuclear cells. Pelvic mucosa normal. No submucous infiltration. Innumerable Gram-negative bacilli in the tubules ; a few in the glomeruli. Left : in an occasional glomerulus some increased cellularity due to round cells ; in some such cases a few similar cells in a neighbouring tubule. Otherwise negative.

Group II.

Case 22. Boy, 8 months, admitted in September. Acute diarrhœa on September 13th. Admitted September 20, and died next day. T. 102° to 104.2°. W.B.C. 16,000. Urine loaded with pus. *Autopsy.* Head not examined. Acute colitis present. Kidneys together 25.6 grams ; externally normal ; on cut surface yellowish lines parallel to the striæ in pyramids but not extending into cortex ; no abscesses. Pelvis slightly congested. Bladder normal. *Microscopic.* Some glomeruli normal ; others congested ; still others unduly cellular owing to an accumulation of mononuclear cells, some free in the capsular spaces. Cells of lining epithelium of Bowman's capsule swollen in some cases. No cells in tubules. Pelvic mucosa, submucosa, and muscularis, and peripelvic tissues normal. Occasional minute collection of round cells in submucosa of ureter. Bladder normal. *Bacteriology.* Both pelves, B. coli.

Case 23. Girl, 2½ months. Admitted in September. Had never thriven, but no recent change. On admission malnutrition ; congestion of ear drums ; T. 99° ; W.B.C. 11,900 ; urine not examined. A few hours after admission the temperature 105.6°, and range thereafter 100° and 106°. Fourth day ; urine, trace of albumen, many hyaline, granular, pus, and cell casts, leucocytes, and urinary tract epithelial cells. Died eighth day. *Autopsy.* Head not examined. Acute entero-colitis, and bronchopneumonia. Kidneys, 27 grams each ; external and on section normal. Pelves slightly injected. Ureters and urethra patent. Bladder, slight injection of fundus. *Microscopic.* Congestion and cloudy swelling, with hyaline material in some tubules. Slight perivascular infiltration in pelvis. Ureter and bladder normal.

Case 24. Boy, age 2 years. For three weeks " pneumonia, convulsions and sore throat." On admission not very ill ; rachitic ; lung signs indefinite ; chronic left otitis media ; T. 100° ; W.B.C. 3,800 ; urine, few pus cells, granular and cellular casts. Condition same for six days. Seventh day refused food, vomited. Suppression of urine. Next day ; urine, albumen, granular and cellular casts, and numerous pus cells ; W.B.C. 21,000. Died that night. Temperature only twice up to 102°. *Autopsy.* Head not examined. Bronchopneumonia present. Kidneys ;

20 grams each ; externally and on section normal. Right pelvis and ureter moderately hyperæmic. Bladder mucosa hyperæmic about trigone. *Microscopic.* Slight hyperæmia and œdema. Pelvis, ureter, and bladder normal.

Case 25. Girl, age three months. Had never thrived ; loose, green stools ; vomited occasionally. For three weeks nasal discharge and cough. On admission ; malnutrition, nasal discharge and cough ; T. 99° ; W.B.C. 7,100. Second day : T. 104° ; acute otitis media. Third day ; paracentesis ; W.B.C. 9,100 ; left kidney now palpable ; urine, trace of albumen, few leucocytes, many epithelial cells, occasional cast. B. coli grown from urine, and again on sixth and seventeenth days. Eleventh day : both kidneys palpable ; strabismus ; persistent vomiting. Spinal fluid normal. Blood culture sterile. Fifteenth day : distention. Phthalein on eighteenth day 21%. Died next day. Throughout, temperature ranged widely, becoming higher from eleventh day on. Urine never more than a few leucocytes. *Autopsy.* Moderately extensive bronchopneumonia. Kidneys together 38 grams ; normal. Pelves normal. *Microscopic.* Extreme congestion, minute blue granules in the interstitial tissue ; no infiltration ; no cells in tubules. Pelvic and ureteral mucosa and submucosa normal. Bladder, patchy congestion of submucosa, and one small hæmorrhage. Over latter point mucosa had been shed off. *Bacteriology.* Kidney, B. coli communis and streptococcus fæcalis.

Group III.

Case 26. Girl, 10 months, admitted in June. Cough, and had done badly for five months and otorrhea for indefinite period. On admission malnutrition, double otitis media, empyæma, urine, loaded with pus. Empyema drained (bacillus influenzæ, Pfeiffer). Urine, para-colon bacillus. Two months in hospital ; rarely any fever, never above 100° ; urine always same. *Autopsy.* Head not examined. Chronic empyema, pneumonia, myocarditis present. Kidneys together 60 grams ; normal except for congestion. Pelvis normal. Ureter somewhat dilated, but mucosa normal. Bladder distended, but mucosa normal. *Microscopic.* Block 1 : glomeruli normal ; cortex very slightly involved ; large areas of leucocytic infiltration along medullary rays ; tubular degeneration; pelvis not seen. Block 2 : glomeruli normal ; small collections of mononuclear cells and polymorphonuclear leucocytes in interstitial tissue : some tubules crowded with pus cells ; slight round cell infiltration of the submucosa of pelvis. Block 3 : glomeruli normal ; here and there in interstitial tissue of cortex foci of cells, varying in number from half a dozen to two or three hundred, the chief cell type a large, round cell, with an irregularly ovoid, vesicular nucleus ; tubular degeneration ; pelvic mucosa ragged, and largely shed off, at angle of reflection submucosa extensively infiltrated with cells similar to those in interstitial tissue of cortex. Block 4 : appeared to be process of healing ; contour of surface rolling,each roll representing a zone of normal glomeruli, granular, empty, dilated tubules, and normal interstitial tissue, while in depressions, glomeruli smaller than in intervening zones, yet no definite change, tubules compressed, and lumina filled with a homogenous substance, interstitial tissue infiltrated with round cells with some tendency to focal accumulation : pelvic mucosa and submucosa normal. Bladder normal.

Case 27. Girl, 17 months, admitted in August. Thirty-nine days ago, nausea, distention, occasional vomiting, fever at times 104.5°. Symptoms persisted, and there were added, irritability, hyperæsthesia, and some looseness of the stools. No cold or cough, nor any urinary symptoms. In hospital : irritable ; recent loss of weight ; ears and chest normal ; abdomen slightly distended ; kidneys almost to crests of ilia, soft, irregular not tender ; bladder almost to umbilicus ; urine, albumen, pus, hyaline and cellular casts, red blood cells ; B. coli grown from it ; T. 101° ; W.B.C. 22,800 ; phthalein 15%. Died on the ninth day. Temperature range 99° to 101°, and once 102°. Urine, pus on all examinations. *Autopsy.* Head not examined. No pathological lesion outside urinary tract. Kidneys 80 grams each ; flabby ; capsule strips fairly easily, but carries some bits of kidney tissue with it ; surface pale red, studded with minute hæmorrhages, small groups of abscesses, and areas of loss of substance ; on section, abscesses largely restricted to surface, a few in renal columns ; many tubules distended with pus ; pyramids quite red. Pelvis deeply injected, but no pus. Ureters slightly distended and rough. Bladder greatly distended

and vessels engorged. Walls of urethra injected. *Microscopic.* Block 1: capsule normal; interstitial tissue œdematous, and, in medulla, congested and slightly infiltrated with small mononuclear cells; glomeruli congested, some containing hyaline globules; tubular epithelium swollen; pelvic mucosa normal, while submucosa contained a few small and large round cells immediately below the epithelium, and more marked collections about the blood vessels. Block 2: in addition to above, one triangular area about 0.5 cm. wide of tremendous polymorphonuclear infiltration and of necrosis, bulging surface and extending to tip of calyx. Block 3: several smaller and more diffuse areas of polymorphonuclear infiltration; many tubules filled with pus. Block 4: Capsule had been stripped off, and appeared to have carried away some kidney tissue at certain points. Travelling along cortex one passed through a zone in which tubules were dilated but empty, glomeruli appeared unduly cellular, and contained the same hyaline masses seen in other sections, but with no cells in the capsular space, and the interstitial tissue showed a slight increase in small mononuclear cells. Next came a zone of more marked infiltration, congested glomeruli, and smaller tubules with more degenerated epithelium. This formed a boundary to an area of complete disintegration, where nothing remained but a few scattered wandering cells in a granular structureless mass. There were three such zones of disintegration in the section, each just visible to the naked eye. Running through the medulla from the deeper border of these areas towards the pelvis, were three narrow strips of a pinkish, structureless nature, in which the tubular elements lay far apart, and through which were growing young fibroblasts. In addition there were clumps of small round cells scattered through the medulla. The pelvic mucosa was normal, the submucosa showing the same changes as were seen in other blocks. The mucosa of the beginning of the ureter had been shed off. There was submucous hæmorrhage, and rather more marked infiltration. A section of the ureter from farther along its course showed a normal mucosa with perivascular infiltration of the submucosa. The lumen contained inflammatory debris, in which at least 90% of the cells were polymorphonuclears. A section of the uretero-vesical junction showed some irregularity of the mucosa, with slight submucous round cell infiltration. Section of the bladder and of the vesico-urethral junction showed only mucosal irregularity.

Case 28. Boy, 7 months, admitted in February. For several days baby had been drowsy, and had vomited. On admission: malnutrition; convulsive movements of hands and feet; kidneys palpable but not considered enlarged; T. 104°; W.B.C. 23,600; urine, pus and few red blood cells; Culture of urine, gram-negative bacillus. Phthalein 56%. Vomiting increased; T. 100°—105°. Died on ninth day. *Autopsy.* Small area of lobular pneumonia. Head not examined. Kidneys: 40 grams each; capsule strips easily; surface pale with numerous yellowish white, slightly irregular, and slightly raised areas; cortex pale, glomeruli not seen; striations regular in cortex, but in pyramids disturbed by roundish, yellowish white, opaque patches; pelvis smooth and delicate, and no sign of inflammation. Ureters normal. *Microscopic.* Block 1: congestion and cloudy swelling. Block 2: slight increase in the mononuclear cells in the interstitial tissue. Block 3: glomeruli congested, an occasional one containing one or two red blood cells or a mononuclear cell in the capsular space; pelvic mucosa irregular, submucosa congested; small submucous hæmorrhage over tip of a papilla. Block 4: area of polymorphonuclear and round cell infiltration running through pyramid parallel to tubules. Block 5: slight congestion, no acute inflammatory foci, and, for the greater part of section slight degree of tubular dilatation, especially in cortex, with flattening of epithelium; three areas just visible to the naked eye, two in cortex, and one in medulla, where tissue appeared more condensed than elsewhere; tubules here collapsed, an occasional one containing a small amount of homogeneous pink substance. Interstitial tissue increased by presence of old, and young fibroblasts, and small round cells with a dark staining nucleus; one cortical area at the surface, which was here depressed; in the other cortical area two glomeruli showed slight epithelial proliferation. One collecting tubule near tip of papilla contained a mass of cells, approximately 70% being large cells with a large vesicular nucleus, 25% polymorphonuclear leucocytes, and 5% small cells with a dark staining nucleus.

Case 29. Girl, 7 months, admitted in May. Had not voided for twenty-four hours, face, hands and feet swollen. On admission: moderate œdema of hands and feet; ear drums slightly

injected ; T. 98.6° ; urine, albumen, pus cells in clumps, red blood cells, and casts. B. coli grown from urine. Phthalein 45%. W.B.C. 13,000. Afebrile for four days ; œdema decreased ; urine approached normal. Temperature then began to rise. Fifth day, W.B.C. 17,500 ; œdema marked ; pyuria increased ; diarrhœa set in. On thirteenth and fourteenth days T. 105°. Temperature rapidly subsided, œdema cleared up, and baby appeared well. Remained in hospital another month, during which time urine showed only an occasional leucocyte. Went to a convalescent home. During five weeks there had otitis media for a few days, and from time to time an unexplained rise in temperature. Urine normal. Then temperature to 104° ; urine contained albumen, pus, and casts ; W.B.C. 29,500. Readmitted to hospital, and died the same day. Her death took place three months from her first admission to hospital. *Autopsy.* Head not examined. Lungs and intestines normal. Left kidney 20 grams; renal substance, pelvis and ureter normal. Right kidney : in pyramid of lower pole a yellowish area measuring 2×7 mm., and in posterior half of kidney a small, circular, reddish elevated, area about 6 mm. in diameter, and of uniform consistency, neither hard nor soft. *Microscopic.* Glomeruli congested. Clumps of leucocytes in collecting tubules. In one section an area about 1 mm. in diameter of intense polymorphonuclear infiltration in cortex. Only evidences of interstitial involvement in the remaining sections were a few groups of small round cells. Pelvic mucosa and submucosa normal.

Case 30. Boy of 22 months. At 14 months admitted to hospital with congenital lues. Urine normal. T. 99° to 100°. W.B.C. 21,000. A few days later, cough and high fever. Urine normal, chest negative. Temperature high for twelve days, and during this time urine first showed albumen, with many mononuclear cells and a few polymorphonuclears then many pus cells. Œdema developed, which persisted about nine days. Temperature then fell, and urine cleared up, though for two and a half months there were always a few cells. He was discharged from hospital, did well for five months, then developed pneumonia, was brought to the hospital, and died there. *Autopsy.* Lobar pneumonia. Kidneys, normal, pelves and bladder. *Microscopic.* No scarring. Pelvic mucosa submucosa and muscularis normal. Peripelvic fat contained an increased number of mononuclear cells.

LEUKÆMIA IN INFANCY AND EARLY LIFE.

BY

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During a study of the diseases of the blood in infancy and early childhood, I was struck by the absence in the literature of any analysis of the symptomatology and blood picture of leukæmia covering a large series of cases. The following paper constitutes such an analysis. It is based on the records of 100 cases of leukæmia, consisting of 91 taken from the literature, 8 cases (hitherto unpublished) observed in the Royal Hospital for Sick Children, Glasgow, and one case which I was allowed to study under the care of Professor Monro in the Western Infirmary, Glasgow. All the patients in this series were under 8 years of age. The greatest care has been taken in their selection so that there could be little doubt regarding the diagnosis, and I consider that they permit of an accurate and comprehensive description of the blood picture and symptomatology of the condition. The selection of examples of myelocytic leukæmia was especially difficult because a number of the cases reported as examples of this disease would almost certainly appear to be cases of severe anæmia in childhood or the so-called von Jaksch's Anæmia.

The general symptoms of all varieties of leukæmia are very much alike and they will, therefore, be treated together. The blood pictures will, however, be described separately.

Nomenclature. In this paper the different varieties of leukæmia have been classified according to the most prominent type of abnormal cell found in the blood stream. For purposes of classification the terms " lymphatic " and " myelogenous " are, in my opinion, hardly suitable, as they suggest that in the one case the origin of the disease is in the lymphatic system and in the other in the bone marrow ; whereas it is nowadays generally admitted that in both types the pathological process is primarily located in the bone marrow. The terms " lymphocytic " and " myelocytic " have, therefore, been adopted. The third variety of leukæmia, viz. : lymphoidocytic, has been so named in preference to " myeloblastic," as in this type the large lymphoid cells with deeply staining cyptoplasm frequently are too primitive to give an oxidase reaction and, therefore, strictly speaking, they cannot be called myeloblasts. They are still undifferentiated leucoblasts. The lymphoidocytes (hæmohistioblasts of Maximov) are multipotential and may differentiate into lymphoblasts or myeloblasts ; they are encountered in the blood stream in most cases of leukæmia in childhood.

Ætiology.

It is not proposed to enter into a discussion of the special ætiology of leukæmia, even if such were possible. Only the general ætiological features will be considered.

Age. In the following table the age incidence is shown.

TABLE I.

Age in Years	1	2	3	4	5	6	7	8
Lymphocytic	12	13	8	16	8	6	5	2
Myelocytic	7	4	2	0	0	3	0	3
Lymphoidocytic	0	1	2	1	2	2	1	2
TOTAL	19	18	12	17	10	11	6	7

From this table one interesting fact emerges ; namely that there are roughly twice as many cases of leukæmia occurring during the first four years of life as occur during the subsequent four years. In certain of the cases (for details of which see appendix) the age of the infant when it came under observation was less than two months and it is possible that these are examples of congenital leukæmia. Case No. 63 came under my own observation in Professor Findlay's wards and the history seemed to date from birth. In not one of these cases did the mother suffer from leukæmia. It is well known, of course, that women the subject of leukæmia have given birth to normal children and I know of no instance having been reported in which a leukæmic child was born of a leukæmic mother. These facts militate against the theory that leukæmia is infective in origin and are more in keeping with the view that it is related to the malignant processes and is, as Banti calls it, " a sarcoma of the blood."

Sex. In 94 cases the sex was stated and of these 62.87 per cent. were males. This is in accordance with the statements generally made that the disease in adult life is more common in the male subject.

Symptomatology.

Leukæmia may be either insidious or abrupt in its onset. In the former case the patient gradually becomes less active ; he may be lethargic and somnolent ; he is frequently irritable and suffers from loss of appetite ; he tends to lose weight and, as a rule, he becomes pale. These prodromal symptoms may persist for one or two months and during this stage the diagnosis of the disease is difficult, but, sooner or later, increasing pallor, hæmorrhages, enlargement of the spleen or of the superficial lymphatic glands will appear and suggest some grave disorder of the blood.

When the onset is abrupt the patient may be suddenly stricken down with fever and great prostration. On examination neither the spleen, liver, nor superficial lymphatic glands may show any palpable enlargement and the only symptoms likely to suggest the possibility of leukæmia may be a purpuric rash or a severe attack of epistaxis. However, even in the cases with the most sudden onset, the patient generally lives long enough for the majority of the main clinical features of the disease to manifest themselves.

The following table illustrates the symptoms of leukæmia in the order of their frequency. In a regrettable number of instances no note has been made to indicate the presence or absence of a particular symptom, and it has been assumed that it was absent if not mentioned.

TABLE II.

Analysis of Symptoms.	Present.	Absent.
Enlarged Spleen	92	7
Enlarged Glands	84	13
Hæmorrhages	78	8
Fever	70	7
Enlarged Liver	70	19
Digestive Disorders	44	3
Gingivitis and Stomatitis	37	7
Cardiac Murmurs	30	9
Enlarged Tonsils	24	11
Albuminuria	20	20
Œdema	19	13
Dyspnœa	17	3
Pain	16	11
Retinal Changes	12	6

In Table 2 it will be observed that there are five chief symptoms, viz. :— splenomegaly, enlargement of the lymph glands, enlargement of the liver, hæmorrhages and fever. The other symptoms, although they may constitute an important part of the general picture in individual cases, are of relatively infrequent occurrence.

(1) *Splenic enlargement.* Enlargement of the spleen *per se* during the first four years of life is of little diagnostic significance for it is well known that in many examples of tuberculosis and syphilis the spleen becomes palpable and may even appear as a very large mass in the abdomen. In the more severe forms of anæmia the spleen is almost constantly palpable, although the degree

of enlargement bears no relation to the severity of the anæmia. Enlargement of the spleen, however, appears to be the most constant feature of leukæmia during childhood and it is therefore advisable to make a blood examination in every case presenting this symptom. The spleen often alters slightly in size during the course of the disease and when its volume diminishes, as it does after a hæmorrhage or an attack of diarrhoea, the parents sometimes offer the opinion that the child is looking better and that its appetite has improved. Again, during the last few days of the illness it is in many instances noticeable that the spleen decreases in size and this alteration may be associated with a similar diminution of the superficial lymphatic glands and with a fall in the white-cell count.

(2) *Glandular Enlargement.* Table 2 also shows that in all but 13 cases there was some degree of glandular enlargement, although in a number of the children the increase was either very slight or limited in extent. The occasional absence of all enlargement, not only of the superficial lymph nodes but also of those more deeply placed, even at post mortem examination, is important since it certainly points to the bone marrow as the site of the primary lesion. Nowadays it is an accepted fact that the blood is never leukæmic until definite changes characteristic of the disease have taken place in the bone marrow, and the occasional instances of leukæmia which arise from time to time showing no enlargement of the glands " go to prove that acute leukæmia, whether lymphoid or myelocytic, is due to changes in the bone marrow, the other hæmopoietic organs being involved, if at all, secondarily." This is in accordance with the opinions expressed by Neumann, Walz, Pappenheim, Brandenburg and others.

When glandular enlargement is present it is most commonly observed during life in the neck. Post mortem the mesenteric glands are almost constantly found to be enlarged, but during life it is not always possible to detect them with certainty. The mediastinal and bronchial glands are also frequently involved and may give rise to distressing symptoms.

(3) *Hæmorrhages.* A petechial rash is one of the commonest symptoms of leukæmia. The eruption may appear all over the body or it may be limited to a small area. Frequently it occurs in the form of successive crops coming on for no apparent reason and bearing no relation to the severity of the disease. The parents sometimes notice that the child " bruises easily " and during the course of the illness large extravasations may take place. Probably the commonest site for these ecchymoses is in the region of the sacrum. Bleeding from the mucous membranes is also common. In the large majority of cases there is hæmorrhage from the gums which occurs as a persistent oozing of blood and may be a prominent factor in the production of the anæmia. Bleeding from the gums may be the principal symptom and lead to a faulty diagnosis of infantile scurvy. Epistaxis is another common symptom and when it takes place it is usually severe, prolonged, and likely to recur. Bleeding from the

bowel is quite common and hæmatemesis occurs in a few cases. Hæmaturia is rare. In this series the percentage of cases in which hæmorrhages occurred is as follows :—Lymphocytic leukæmia, 93·8 per cent. ; Myelocytic leukæmia, 78·6 per cent. ; and Lymphoidocytic leukæmia, 75·0 per cent.

The explanation of this tendency to hæmorrhage is somewhat obscure. The more severe forms of purpura are generally associated with a marked decrease in the number of blood platelets and such is usually found in lymphocytic leukæmia. On the other hand, there is also a marked hæmorrhagic diathesis in the other forms of leukæmia although studies of these in the adult reveal the fact that the platelets may be normal or even increased in number. No figures showing the platelet count in myelocytic leukæmia during childhood are available. However, in most examples of moderately acute leukæmia (and all leukæmias of childhood may be regarded as acute) the bone marrow is so crowded with leucoblastic cells that the megakaryocytes, from which the platelets are understood to be formed, come to be decreased in number. But, even when present, thrombocytopenia constitutes only a partial explanation of the tendency to bleeding, and it would seem not improbable that some abnormal change in the vascular endothelium plays an important role.

(4) *Fever.* Some degree of fever was present in 70 cases of this series ; in 7 cases it was stated to be absent and in 23 it was not mentioned. There is nothing characteristic about the temperature chart of a case of leukæmia. Sometimes the fever is of the continued type, sometimes it is remittent or intermittent and, speaking generally, it is capricious and irregular. Occasionally the temperature may rise to 105° F. At the beginning of the illness in children there is usually some degree of fever, and this is one of the points which makes the clinical picture so similar to that of an acute infectious disease. Towards the termination of the disease the temperature may fall and be accompanied by a decrease in the size of the spleen, liver and lymphatic glands, and a fall in the number of leucocytes in the blood. On the other hand, the patient may die with hyperpyrexia suggesting some toxic action on, or a leukæmic infiltration of, the pons varolii.

The ætiology of the disease being unknown, it is impossible to explain the fever. It may however be that (1) it is a manifestation of the systemic reaction to a specific infection ; (2) it is the result of some secondary infection with pyogenic organisms ; (3) it is due to the digestive disturbances which occur during the course of the illness ; (4) it is due to the action of degenerated leucocytes on the heat centres (Treadgold [2]).

(5) *Hepatic enlargement.* Enlargement of the liver was present in 70 instances in this series, and in 19 it was stated that the organ was not enlarged. How accurate these figures are it is difficult to say. In young children the lower border of the liver can usually be felt half to one inch below the costal margin, and it is quite possible that this condition has been recorded as an actual enlargement of the liver in a proportion of the cases. However, in the majority of cases in which a post-mortem examination was performed

the liver was found to be definitely enlarged. The relative frequency of hepatic enlargement in the three varieties of leukæmia was as follows :—Lymphocytic leukæmia, 80·6 per cent; Myelocytic leukæmia, 75·0 per cent.; Lymphoidocytic leukæmia, 66·6 per cent.

(6) *Digestive disturbances.* Symptoms referable to the gastro-intestinal system were present in 44 cases ; in 53 cases no note was made, because these symptoms were either absent or not considered significant. Such symptoms were anorexia, diarrhoea, constipation and vomiting. Hæmatemesis and melæna were present in a few patients. The tongue was generally furred and the gums were frequently swollen and bleeding. 37 children in this series suffered from stomatitis and gingivitis. The tonsils were enlarged in 24 cases ; in 11 there was stated to be no enlargement and in 65 no reference was made to the condition of the tonsils.

(7) *Cardio-vascular symptoms.* In a considerable number of cases mention was made of the condition of the heart and pulse. The pulse was generally soft, of low tension and increased in rate. The heart was sometimes found to be enlarged, and a murmur or bruit coincident with ventricular systole was heard in a proportion of the cases (30 in this series). Post-mortem examination in no case revealed endocarditis nor was there any record of infiltration of the auriculo-ventricular bundle such as might have produced heart block.

(8) *Genito-urinary symptoms.* In 3 cases it was stated that the kidneys were large and easily palpated (Nos. 25, 28, 32) but with these exceptions there was no clinical note of the size of these organs in any of the series. In several instances post-mortem examination showed a considerable enlargement of the kidneys. Albuminuria was not uncommon but seldom appeared to be present to the same degree as in acute nephritis. The uric acid output was increased, due to the katabolism of the excessive endogenous protein associated with the leucocytosis. Hæmaturia was rare.

(9) *Respiratory symptoms.* Dyspnœa was not an uncommon symptom. It may be due to enlarged glands in the neck pressing on the trachea or larynx. This was the cause of death in Case No. 4 Again, dyspnœa may be due to enlarged bronchial and mediastinal glands pressing on the recurrent laryngeal nerve or on one of the larger bronchi. In infants with leukæmia the tonsils are often enlarged with, presumably, hypertrophy of the nasopharyngeal adenoid tissue, and it is quite possible that these factors play a part in the production of the dyspnœa. Finally, dyspnœa may exist as a manifestation of the severe degree of anæmia which is so constantly present.

A mild bronchitis is probably present in the majority of cases but it usually causes no symptoms of importance. Some degree of œdema of the lungs is always present and is associated with the anæmia. Pneumonia may occur at any time during the course of the disease, but, as a rule, it is not associated with the usual reactions seen in the healthy subject and, not infrequently, it may be discovered only at the post-mortem examination.

(10) *Skin.* One of the most constant features of leukæmia is the occurrence of hæmorrhages either into or beneath the skin. These phenomena have already been described. Sweat rashes are not uncommon in childhood and when present in cases of leukæmia probably bear no relation to the disease. Herpes occurred in one of this series (Case No. 20) and ulceration of the skin occurred in Case No. 17. Oedema of the skin and subcutaneous tissues was present in 19 instances. The œdema may be generalised and associated with ascites or it may be limited to the face or ankles. In a proportion of cases tumours may be present in the skin, the condition called "Nodular leukæmia" by Ward ([3]) who has collected a number of examples. According to Ward the nodules probably arise from the scattered foci of lymphoid tissue which occur throughout the meso- and hypo-blastic tissues. The nodules do not appear in the epiblastic tissues such as the epidermis or the central nervous system, although they frequently grow from the subjacent fibrous tissue of the skin (Case No. 54) and the dura mater. The cutaneous nodules differ greatly in size and colour. They may be as small as a pin's head or as large as a cricket ball and their colour is dependent upon their depth from the surface and whether or not they have been the seat of interstitial hæmorrhages. The nodules may be present throughout the alimentary canal. Finally, they occur in connexion with the bones, particularly the bones of the head and it is these tumours which frequently have the green colour which has been responsible for their having been named Chloroma (Cases Nos. 89, 95). In some cases the usual greenish colour may be absent ; in others it may fade very rapidly after removal of the tumour, but it can sometimes be brought back by immersing the tissue in hydrogen peroxide. The nodules, wherever placed, may become smaller in size or even disappear suddenly. Chloromata may occur with any of the three types of leukæmia, but they seem to be most commonly associated with the lymphocytic and lymphoidocytic varieties.

(11) *Retinal changes.* It is unfortunate that in 82 of this series no mention has been made of the appearances of the fundus oculi. In 6 it was stated that there was no abnormality and in 12 certain changes were observed. The commonest lesion consisted of one or more small retinal hæmorrhages (11 cases). In one case pallor of the disc and fundus was noted and in another, in addition to retinal hæmorrhages, there was a neuro-retinitis.

Course of the Disease.

The duration of leukæmia in infancy is always short and, therefore, the disease must be regarded as a uniformly acute process at this time of life. Seldom, are remissions of the symptoms observed. Once the disease has developed, the patient passes steadily downhill and within 2 or 3 months death takes place. The following figures show the average duration of the illness in 73 per cent. of this series :—

Lymphocytic leukæmia	2·0 months.
Myelocytic leukæmia	4·3 ,,
Lymphoidocytic leukæmia	2·1 ,,

The apparent relative chronicity of the disease in the myelocytic form is largely to be accounted for by the protracted course of case No. 78, in which it is stated that the child lived for 2 years after leukæmia had developed.

The figures in this series seem to show that in children the average duration of the illness varies but little whether the large or small lymphocytes dominate the blood picture, or whether the case is a definite lymphoidocytic leukæmia.

The Blood.

(*a*) *Lymphocytic Leukæmia.*

Seventy per cent. of this series were examples of lymphocytic leukæmia. The blood flows easily from a prick in the finger or lobe of the ear. It is paler and more watery than in the healthy subject and, as a rule, it does not show the normal tendency to rapid coagulation.

Serum. The serum may appear quite normal, or it may contain a moderately large quantity of fat, as in Case No. 56. In none of the cases in this series was the Wasserman reaction said to be positive. A positive Widal reaction was obtained in Case No. 6. In some examples the serum may be frankly jaundiced. In 7 cases a streptococcus was said to have been cultivated from the blood and in Case No. 57 I isolated a streptococcus which multiplied rapidly under anærobic conditions but which, although it survived, grew less freely under ærobic conditions. It must be remembered, however, that streptococci may be isolated quite frequently during the terminal stages of many illnesses in childhood.

Red Cells. The total red cell count is always decreased and towards the end of the illness it may fall below a million per cubic millimetre (Cases No. 8, 13, 40, 54, 64). The average red cell count was 1,946,000. Irregularity in size and shape of the corpuscles is present and polychromasia and basophile stippling are common features. Nucleated red cells are generally present but, as a rule, they are scanty in number. The erythrocytes stain well and the average hæmoglobin content in this series was 31 per cent., which gave a colour index of 0·816.

White cells. In this series there was a leucocytosis in 58 cases ; in 8 the total white cell count was either decreased or within normal limits ; and in 4 no note was made. The average leucocyte count was 210,245 per c.mm.

It would appear that in those cases in which the onset is not very sudden and in which the patient does not seem to be seriously ill the white cell count is high and may even exceed a million per cubic millimetere (Cases No. 10, 31, 41, 52). When the onset is abrupt and the patient is prostrated and obviously in a perilous condition the white cell count may not be raised and, in fact, there may even be a definite leucopenia (Cases No. 17, 22, 30, 54, 58, 62, 65). During the last few days of the illness the leucocyte count almost always falls and this is regarded as a grave factor in the immediate prognosis,

The one constant feature about the blood in lymphocytic leukæmia is the high *relative* increase of the lymphocytes. Whatever the total white cell count may be, the lymphocytes are always relatively in excess of normal and in this series averaged 94 per cent.

Characters of Lymphocytes. The type of lymphocyte which dominated the blood picture was noted in 52 of this series. In the majority of cases (61·54 per cent.) the micro- and meso-lymphocytes were the predominating cells. In these forms the nucleus stains deeply and the cytoplasm is scarcely visible. In some examples (38·46 per cent.), however, the large lymphocytes were present in the greatest proportions. Such cells have a rather paler nucleus than the small forms and in it one or two nucleoli may be observed. The cytoplasm is not abundant and seldom if ever contains the azurophil granules which are so commonly seen in the lymphocytes of healthy blood.

In films from every case of lymphocytic leukæmia lymphoidocytes may be found. Sometimes they are present in quite large numbers and the blood picture represents an intermediate stage between lymphocytic and lymphoidocytic leukæmia.

A large number of the lymphocytes seen in a film of lymphocytic leukæmia present some abnormality which leads to their being regarded as pathological cells in contradistinction to the healthy lymphocytes which appear in a simple lymphocytosis. Such abnormalities consist of extreme scantiness of the cytoplasm, vacuolation of the cytoplasm, changes in the nucleus indicative of karyolysis and the familiar " shadow " or " basket " cells which are found so often in cases of leukæmia with a high cell count. The latter forms represent the penultimate stage of the lymphocytes which have undergone cytolysis, although in a certain proportion they are due to a breaking up of the already fragile lymphocytes in the making of a very thin film.

(*b*) *Myelocytic Leukæmia.*

Red Cells. The average total red cell count in this series was 2,114,800 which is about the same as that observed in the lymphocytic variety. The average hæmoglobin content was 31·8 per cent, giving a colour index of 0·76.

White Cells. The average white cell count was 139,020 per c.mm. This figure is much lower than that obtained in the cases of lymphocytic leukæmia in this series. In no case was there a leucopenia.

Apart from the clinical features of these cases, the characteristic which compelled a diagnosis of leukæmia was the high proportion of myelocytes present in the blood films (average 32 per cent.). Such a myelocytosis is not observed in any other condition in infancy or childhood. Further, post-mortem examinations were performed in 58 per cent. of these cases and the diagnosis was stated to have been confirmed by the appearances observed.

The following figures represent the average differential count of the white cells obtained from this series :—

Polymorphonuclears	38·7%
Eosinophils	3·6%
Lymphocytes	25·0%
Myelocytes	32·0%

It is somewhat remarkable that no mention has been made of the proportion of basophils because myelocytic leukæmia essentially consists of an absolute increase of *all* the cells of the granular series.

There is one interesting fact to be learned from these figures, viz. : that in myelocytic leukæmia in infancy and early childhood there is a large *absolute* lymphocytosis which accompanies the increased output of the normal and abnormal cells of the granular series.

(c) *Lymphoidocytic* (*Myeloblastic*) *Leukæmia.*

In this series there were 11 cases.

Red Cells. The average red cell count was 2,066,400 per c.mm. The hæmoglobin content was 31 per cent. and the colour index was 0·775.

White Cells. In this form of leukæmia the white cell count was low in comparison with the other varieties : the average here being 47,962 per c.mm. The average proportion of lymphoidocytes (or myeloblasts) present in a differential count was 58 per cent. A leucopenia was observed in cases No. 91 and 93. An average differential count gave the following figures :—

Polymorphonuclears	9·3%
Eosinophils	2·0%
Lymphocytes	22·5%
Myelocytes	4·6%
Lymphoidocytes	58·0%

The lymphoidocytes are regarded as being the parent cells of both the granular and non-granular series and thus they may differentiate into myeloblasts or lymphoblasts. The lymphoidocytes do not give a positive oxydase reaction and if the preponderating cell in a blood film from such a case gives this reaction it indicates that differentiation is taking place towards the granular series and only then is it justifiable to apply the term myeloblastic leukæmia.

Summary.

An analysis has been made of the clinical features of 100 cases of leukæmia occurring in children under 8 years of age. It is shown that the symptomatology of all three varieties of the disease is more or less the same and that the commonest features are enlargement of the spleen, lymphatic glands and liver, along with some degree of fever and various forms of hæmorrhage. The disease runs an acute course and the patient rarely lives more than 2 months after the diagnosis has been made.

The blood picture shows a marked degree of anæmia and a leucocytosis in all forms of the disease. The leucocytosis is highest in lymphocytic leukæmia and lowest in lymphoidocytic leukæmia, although in either of these varieties an actual leucopenia may be present. 19 cases of myelocytic leukæmia have been analysed and it is shewn that, in addition to a very high myelocyte count, there is also a large absolute lymphocytosis.

In conclusion, it gives me much pleasure to acknowledge with gratitude the encouragement and kindly criticism which I have received from Professor Leonard Findlay at whose suggestion this investigation has been made.

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TABLE I.

(see over)

TABLE I.

CASES OF LYMPHOCYTIC LEUKÆMIA.

No.	Author.	Sex.	Age in Months.	Duration in Months.	Enlarged Spleen.	Enlarged Liver.	Enlarged Glands.	Fever.	Hæmorrhages.	Retinal Changes.	Dyspnœa.	Digestive Symptoms.	Albuminuria.	Heart Murmurs.	Stomatitis.	Pain.	Œdema.	Enlarged Tonsils.	P.M. Examination.	Red Cell Count.	Hb. %.	White Cell Count.	Lymphocytes. %	Predominant Type of Lymphocyte.
1	Savory	M	54	1½	—	—	+	+	+	+	+	+			+			+	—	2,157,000	35	356,000	96	Large
2	Geissler, Japha	M	60	3	+	+	+	+	—											1,580,000		34,250	97	
3	Chisholm..	M	42		+		+		+														98	
4	Larabee	F	1½	1	+	—	+		+		+	+							—	4,392,000	60	918,000	99	Small
5	Babonneix, Tixier	F	18	2	+		+	+	+		+	+	+		—			—	+	2,950,000	70	43,600	91	Large
6	Rocaz	M	48	1	+		+	+	+			+			+			+	+	1,816,000	30	244,000	96	
7	McCaw	F	20	1½	+	+	+	+	+				+						—	2,200,000	38	818,000	99	
8	Glimski	M	12		+	—	+		+			+			+		+		+	918,760	21	180,416	94	
9	Churchill	M	48	1	+	+	+	+	+		+	+	—	+				+	+	2,740,000	40	52,000	99	
10	Veeder	F	17		+	+	+	+	+				+	—	+			+		3,370,000	55	1,330,000	99	Small
11	Bezy	F	84		+	—	+	+	+		—	+	—			+			+	3,000,000		20,000	95	Large
12	Strauss	M	13	1	+	+	+	+	+			—	—					—	+	2,008,000	25	208,000	97	
13	Condat	F	48		+	+	—	—	+			+			+		+		—	660,000	20	148,000	91	Small
14	Hutchison	F	72	3	+	+	+	+	+	+					+					1,200,000	10	170,000	98	Small
15	Carpenter		42	1	+	+	—						+							1,568,000	15	130,000	99	Small

16	Surmont, Debon		42	4	+	−	+	+	+		+		+		+		+	+		2,433,500		14,375	99	Small
17	Nobel		18		+		+	+	+											1,700,000	25	6,400	79	
18	Comby	F	48	4	+	+	+	+	+					+			+		−	2.164,000		70,680	97	
19	Johnson	M	24	1	+	+	+		+				+		+				+	1,200,000		517,000		Large
20	Whiphan, Leathem	F	24	1	+	+	+	−	+			+			+	+			+	3,000,000	42	20,000	98	Large
21	„ „	M	57	½	+	+	+	+	+	+		+		+	+				+	2,196,000	58	22,800	72	
22	Moussous	M	42	4	+	+	+	−	+	−	+		+	+						1,143,600	21	5,580	99	Small
23	McCrae	M	36	1	+	+	−	+	+			+		−	+		−	+	−	1,760,000	32	60,800	99	Small
24	Forbes, Langmead	M	18	1	+	+	+	+	+				+				+	+	+	1,106,000	15	83,000	91	Small
25	„ „	M	15	1	+	+	+	+	+	−		+	+	+	+			+	+	1,000,000	30	29,000	92	Small
26	„ „	M	24	1	+	+	+	+	+			+							+	1,200,000	20	196,840	98	Small
27	„ „	F	12	1½	+	+	−	+	+			+						−	+	1,000,000		60,000	93	Small
28	„ „	F	7		+	+	+	+	+			+	+						+	2,000,000		321,000	99	Large
29	„ „	M	36	2	+	+	+	+	+	+			+		+			+	+	1,340,000	32	14,000	96	Small
30	„ „	F	42	6	+	−	+	+	−										+	2,550,000		7,500	96	Small
31	„ „	M	30	2½	+	+	+	+	+	+	+		−		+			−	+	3,000,000	35	1,000,000	97	Small
32	„ „	F	39	1	+	+	+	+	+		+	+	+				+	−	+		38			
33	„ „	F	48	2	+	+	+	+	+	+		+	−	+				+		2,284,000	45	61,000	99	
34	Chaney	F	60	6	+	+	+	+	+				−	+				+	−	1,500,000	21	19,000	100	Small
35	„	M	54	1½	+	−	+		+		+	+				+		−	−	2,500,000	45	304,000	96	Small
36	Cheney	M	84	4	+	+	−	+	−			+		+				−	−	2,000,000	15	480,000	96	Small

TABLE I (Contd.).

CASES OF LYMPHOCYTIC LEUKÆMIA.

No.	Author.	Sex.	Age in Months.	Duration in Months.	Enlarged Spleen.	Enlarged Liver.	Enlarged Glands.	Fever.	Hæmorrhages.	Retinal Changes.	Dyspnœa.	Digestive Symptoms.	Albuminuria.	Heart Murmurs.	Stomatitis.	Pain.	Œdema.	Enlarged Tonsils.	P.M. Examination.	Red Cell Count.	Hb. %.	White Cell Count.	Lymphocytes. %	Predominant Type of Lymphocyte.
37	Bradford, Shaw	M	84	2	+	—	+	+	+			+	+		+	+	—	—	+	1,480,000	31	34,400	99	Large
38	Muller	M	48	1	+	+	+	+	+						+	+			+			109,600	97	Large
39	,, ...	M	48	1	+	+	—	+	+						+				—			209,000	98	Large
40	Vermehren	F	3	3	+	+	+		+			+	—						—	739,000		260,000	99	Small
41	Lommell	M	1	1	+	+	+										+		+	1,282,000		1,240,000		Small
42	Mennacher	M	11	5	+	+	+	+	+			+					—	—	+	4,900,000	40	258,000	73	Small
43	McWeeney, Farnan	F	36		+	—	+	+	+				—	—		+	+		—	1,540,000		136,400	97	Large
44	Kakels	M	18		+		+		+				+	+	+				—	2,046,000		682,000	94	Small
45	Morse	F	36	½	+	+	+	—	+			+		+		—		+	—	2,024,000	25	87,400	94	Small
46	Myers	M	51	2	+	+	+	+	+		+	—	—	+	—		—	+	+	1,424,000	25	32,000	97	Small
47	Holscaw	M	11	1	+	+	+	+	+			+	+	—	+	—		+	+	3,200,000		109,000	99	Small
48	Smith	M	1½	½	+	+	+	+			+		+			—	—			2,624,000		189,000	91	Small
49	Lehndorf	M	48	1	+	+	+	+	+						+			+	+	1,690,000	27	69,000	92	Large
50	,, ...	F	16	2	+	+	+		+										+	2,800,000		80,500	92	Large
51	Flesch	M	48	½	+	+	+	+											—	3,000,000		380,000	96	Large

52	Berghinz	F	84	2	−	+	+	+	+						+		+		−	1,300,000		1,100,000	92	
53	Bradley	M	96	2	+	+	+		+						+				−	1,850,000		85,000	97	Large
54	Bunewardene	M	36	6	+	+	+	+	+			+	+	+	+	−		+	+	760,000	11	8,400	85	
55	Haushalter, Richon	M	90	2	+		+	−											+	1,829,000		36,000	83	Small
56	Prof. Monro	M	54		+	+	+	+	+	+	+		−	+	+	+	−	+	−	1,360,000	18	22,900	97	Small
57	R.H.S.C.	F	18		+	+	+	+				+		+	+				−	1,230,000	32	10,200	96	
58	R.H.S.C.	F	54	2	−	−	+	+	+			+		+		+		+	+	2,080,000	30	9,600	96	
59	R.H.S.C.	M	7	3	+	+	+	+	−	+		+	+	+	+				+	1,490,000	14	42,400	88	
60	R.H.S.C.	F	7		+	+	+	−	+			+		+					−	1,630,000	20	47,000	92	
61	R.H.S.C.	F	72	3	−	−	+	+	+		+		+	+		+	+	+	−	1,312,000	35	40,000	96	Large
62	R.H.S.C.	M	66	3	+	+	+	+	+					+	+			+	+	1,260,00	30	3,200	78	Large
63	R.H.S.C.	M	1½	1	+	−	+	+	+	−	−	+	−	−	−	−	−	−	−	3,120,000	70	713,000	94	Large
64	Bartlett		14	2½	+	+			+										+	824,000	20	57,100	94	Large
65	Bass	M	48		+	+	+	+	+	+		+				+			−	1,912,000	32	4,000	96	Small
66	Strauch	M	48	3	+	+	+	+	+		−	+	−	+	−	−	−	+	+	2,200,000		40,000	93	Small
67	Cooke	F	36	¾	+	+	−		+	+									+				89	Small
68	,, ...	M	30	1	+	+	+		+						+			+	+				99	Small
69	Ross	M	78		+	+	+	+	+		+			+		−	+					60,000		Large
70	Acuna	M	72	½	+	+	+	+	+			+	−	−	+	+	+		+	1,500,000	40	250,000	93	Large

TABLE II.

CASES OF MYELOCYTIC LEUKÆMIA.

No.	Author.	Sex.	Age in Months.	Duration in Months.	Enlarged Spleen.	Enlarged Liver.	Enlarged Glands.	Fever.	Hæmorrhages.	Retinal Changes.	Dyspnœa.	Digestive Symptoms.	Albuminuria.	Heart Murmur.	Stomatitis.	Pain.	Œdema.	Enlarged Tonsils.	P.M. Examination.	Red Cell Count.	% Hb.	White Cell Count.	% Polymorphs.	% Eosinophils.	% Lymphocytes.	% Myelocytes.	% Lymphoidocytes.
71	Morse	M	12	1	+	+	+	—	+										—	2,900,000		48,000	46	6	31	21	
72	Lehndorf	M	18	2	+	+	+	+	+				+	+	+		+		+	1,600,000	22	32,000	53	1	33	12	
73	Berghinz	F	96	4	+	+	+	+									+		—	2,000,000		800,000	59	2	9	27	
74	Karsner..	M	30	6	+	+	+		+	+	+	+	—	—	—	—	—		+			19,000					
75	Falconer	M	72		+	—	+	+	—	—				+		—			—	2,260,000	45	146,970	47	5	2	36	
76	Stewart, Campbell	M	72	3	—		+	+	+						+				+	750,000		40,000	45	3	25	27	19
77	Whipham		18		+	+	+	+	+											4,080,000	80	63,400	32	2	5	26	
78	Charon, Gratia..	F	96	24	+	+					+								+	880,000	39	305,000	49			37	
79	Ginsberg	M	30	4	+	+	+		+										+		55						
80	Cassell	M	96		+	—	—		—			+				+	—		—	3,550,000	40	500,000	30	12		69	
81	Goodall	F	2½		+	+	—		+			+		—	+				+	1,100,000		75,000	26	1	24	48	
82	Carpenter		12		+	+	—		+											2,900,000		48,000	47	1	31	21	
83	Zylberlast	M	6	3	+	—	—		—		+	+	—			—			+	2,720,000	35	39,370	32	3	49	26	
84	Menetrier, Aubertin	M	4		+	+	—												—	Whites to reds = 1.4			24		25	42	
85	Weilelerc	M	14	½	+	+	+	+											+	3,317,000		28,000	9	4	41	17	
86	Hirschfeld	M	72	¾	+		+	+		+		+	—	+	+		—		+	800,000		59,000	60		18	23	
87	Benjamin Sluka	M	6	1	+	—	+	+	+			+					+	+	+	1,500,000	30	120,000	27		31	42	
88	Delfosse	F	12		+		+	+	+											1,400,000		25,000				33	
89	R.H.S.C.	F	13	2½	+	+	+	+	+	—			+	+		+	+	—	+	2,080,000	20	115,000					

TABLE III.

CASES OF LYMPHOIDOCYTIC LEUKÆMIA.

No.	Author.	Sex.	Age in Months.	Duration in Months.	Enlarged Spleen.	Enlarged Liver.	Enlarged Glands.	Fever.	Hæmorrhages.	Retinal Changes.	Dyspnœa.	Digestive Symptoms.	Albuminuria.	Heart Murmurs.	Stomatitis.	Pain.	Œdema.	Enlarged Tonsils.	P.M. Examination.	Red Cell Count.	% Hb.	White Cell Count.	% Polymorphs.	% Eosonophils.	% Lymphocytes.	% Myelocytes.	% Lymphoidocytes.
90	Panton, Tidy	M	60	1½	—		—	+				+				+	+			1,930,000	20	13,800	1		1		98
91	Ross	M	72	3½	+	+	+	+	+	+		+		+	+				+	2,377,000	30	6,900	1		23		75
92	„	M	39		+	+	+	+		—				+	—	—			—	1,800,000	28	17,200	19	19			38
93	„	F	66	1	+	+	+	+	+					+	+		+	+	+	2,650,000	30	1,132	2		10	2	86
94	Dallas	F	20	3	+	—	+	—	—			—					—		—	2,253,000	25	36,452	30		49		21
95	Esser	M	96		+	+	+	+	+				—	+			—		+	840,000	35	8,700	21		1	5	24
96	Horwitt	M	60		+	+	+	+	+				—		—		—		—	1,000,000		140,000	2				98
97	Bass	F	96		+	+	+	+			+		—						—	2,080,000	41	134,400	5		15		80
98	Purser	M	36				+	+							+					2,800,000	50	78,000					
99	Nanta and Loubet	F	84		+	—		+	+			+	—	—	+	+			—	2,900,000		20,000					77
100	Stirnimann	F	36	2½	—	—	+	+	+			+	+	+	+					2,100,000	20	70,000	3	2	43	7	44

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THE INDIRECT DETERMINATION OF THE *p*H OF THE BLOOD IN CHILDREN.

BY

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In any indirect method of determining the *p*H of the blood a knowledge of the ratio $H_2CO_3 : BHCO_3$ becomes essential. The sum of these two factors, or the total CO_2, can readily be estimated by an analysis of a sample of blood in the Haldane or the Van Slyke blood-gas apparatus, but the proportion of free CO_2 (H_2CO_3) to the combined CO_2 ($BHCO_3$) is much more difficult to determine.

It has long been known that the tension of CO_2 in arterial blood is approximately the same as that of the alveolar air. Thus, by obtaining samples of alveolar air, one can readily calculate the CO_2 tension in the blood and, by using Bohr's coefficient, arrive at the figure for the free CO_2 content (H_2CO_3). The total CO_2 content less this figure will then represent the combined CO_2 ($BHCO_3$) of the blood.

In infants and children, we have tried various ways of obtaining alveolar air, including the original Haldane-Priestley method as well as that recently used by Henderson[1] in his method of estimating the blood-flow. The results of the CO_2 analysis, however, always confirmed our doubts as to the genuineness of the samples obtained. Consequently, it became necessary to devise some other method for the determination of the CO_2 tension of the blood.

It has been stated that air injected into any body cavity assumes the same partial pressure or tension of oxygen and carbon dioxide as exists in the arterial blood. Argyll-Campbell[2] has injected air subcutaneously as well as intra-peritoneally in rabbits and has demonstrated that the CO_2 content of the air so injected in about one hour becomes the same as that in the alveolar air obtained by the usual Haldane-Priestley method. Haggard and Henderson[3] in a study of the effect of ether anæsthesia on the CO_2 content of air injected intra-peritoneally in dogs have concluded that the tension of the CO_2 in the injected air becomes after a period of time identical with that of the arterial blood. Henderson[1] has also suggested that the same equilibration of gases takes place if air be held in the mouth with the lips closed and the cheeks distended. In this way he obtains samples, the CO_2 content of which is the same as that of alveolar air. We, however, have repeatedly tried this method

of holding air in the mouth but, whether from inexperience or not, we were unable to obtain in ourselves concentrations of CO_2 which fell within the usual limits of normal.

During a conversation with Henderson on this question the possibility was suggested that a figure approximating the CO_2 content of alveolar air might be obtained by injecting air into the rectum and, after allowing time for the diffusion of gases, removing samples for analysis. It is this method and the results obtained by it which form the basis of this paper.

METHOD :—The technique adopted was as follows :—After a simple enema, a rectal wash-out with an 0.5% $NaHCO_3$ solution was given until the return was clear. Then, by means of a catheter and a large (100 cc.) syringe, 100 to 200 cc. of air were slowly injected into the rectum. The catheter was left *in situ*, the free end being clamped. At the end of half an hour a sample was removed in the syringe by means of a three-way stop-cock, care being taken always to discard the air which had been in the catheter and consequently not exposed to the bowel wall. This sample was transferred directly to a Haldane air-gas analysis apparatus and its CO_2 content determined. Subsequent samples were taken every ten minutes for analysis. In later experiments, we found it of value to mix the air at the end of 15 minutes by withdrawing it into the syringe and re-injecting it. The whole procedure can be accelerated by injecting air containing approximately 4% CO_2. Ordinary expired air serves this purpose quite well.

The pollution of the air in the rectum with fæcal gas from the bowel above is, of course, a probable source of serious error. Such fæcal gas, however, would only influence the analysis if it were acid in reaction. If neutral, the gas would simply dilute the percentage in the equilibrating air and so delay the equilibration, but the tension of CO_2 in the rectum would gradually return to that of the blood, provided the air were left sufficiently long in the rectum. Should the polluting gas be acid in character, it would undoubtedly raise the percentage of CO_2 obtained on analysis and it was to obviate this possibility that a preliminary wash-out of $NaHCO_3$ was given. The small amount of $NaHCO_3$ left in the rectum we believe is sufficient to neutralise any polluting acid gas. The presence of any polluting acid gas would cause an evolution of CO_2, but this, of course, would gradually be equilibrated. In our investigations, the interval between the taking of successive samples was never less than ten minutes and any results differing by more than 0.3 from the mean of three successive readings should be accepted with caution. Unfortunately, in infants and in children under two years of age we have found it impossible to prevent the air being expelled around the catheter, even when very small amounts were injected. In children over two years however, no such difficulty was experienced and the procedure did not disturb them in the least. On many occasions, as much as 300 cc. of air was injected without causing the slightest inconvenience.

TABLE I.

Observation No.	Age in Years.	Sex.	Time in Mins. after Injection at which sample was taken.								Average CO_2 Content. Rectal Air.
			30	40	50	60	70	80	90	100	
1	7	F	–	6·0	6·5	6·2	6·4	6·4	6·6	6·4	6·4
2	7	F	5·9	5·6	5·5	5·5	–	–	–	–	5·5
3		M	4·9	6·0	6·0	5·9	6·0	–	–	–	6·0
4	12	M	4·4	5·1	5·9	5·7	6·2	6·6	6·2	6·3	6·3
5	2	M	–	3·7	5·0	5·0	5·0	–	–	–	5·0
6	7	M	5·0	5·0	5·2	6·0	4·5	5·0	4·9	–	5·0
7	10	F	4·8	5·0	5·4	5·0	5·0	–	–	–	5·0
8	9	M	–	–	5·8	6·7	6·6	7·0	6·9	6·9	6·8
9	10	F	4·4	4·3	4·3	–	–	–	–	–	4·4
10	7	F	4·4	5·3	5·4	5·7	5·4	–	–	–	5·5
11	2	M	–	4·8	5·0	4·9	–	–	–	–	4·9
12	4	M	–	5·9	5·7	6·0	5·7	–	–	–	5·8
13	4	M	–	5·3	5·7	5·7	–	5·5	–	–	5·5
14	8	M	4·5	5·0	5·0	5·0	–	–	–	–	5·0
15	8	M	–	–	4·9	5·0	4·8	5·3	5·5	5·3	5·4
16	11	M	5·2	5·5	5·7	–	–	–	–	–	5·5
17	4	M	–	5·8	6·8	6·8	–	–	–		6·8
18	4	M	5·3	5·4	5·8	4·6	5·3	–	–		5·3
19	6	M	–	6·0	6·6	7·2	7·1	7·3	6·7	–	7·0
20	9	M	–	6·0	6·6	6·6	–	–	–	–	6·6
21	6	M	–	4·2	4·2	4·2	–	–	–	–	4·2
22	7	F	–	5·2	5·0	6·4	5·6	6·0	6·5	–	6·1
23	7	F	–	5·3	5·3	6·8	6·3	5·8	5·7	–	5·9

The above table (Table I) gives a few of the results obtained and it is seen that on the whole, the successive readings at ten minute intervals agree fairly well, once the tension has become established. Occasionally for some reason, perhaps an unusual degree of pollution by fæcal gas from above, a high figure is obtained. For example, the 60 minute sample in Case 6 is obviously wrong, but the 70 minute reading shows that equilibration had again taken place. With 100 cc. of air it is usual to get only three samples of 15 to 20 cc. each or,

at the most four, but if the first sample is taken at the 40 minute period a good result can be obtained in almost every case.

In adults, the average normal CO_2 content of alveolar air is approximately 5.5% but owing to the technical difficulty in obtaining good samples, wide variations occur and figures well above or below 5% to 6% are required before much significance can be attached to them. Our results obtained by analysis of rectal air showed a variation of from 4·2 to 7%. Although this variation appears wide, we believe that such does occur in young children. We know that the younger the child the more often and the more readily does the acid-base balance shift and in the routine estimation of the alkaline reserve of the blood one is struck with the wide variations which occur in children who are to all intents and purposes normal so far as their acid-base balance is concerned. If this total CO_2 combining power is so frequently altered, it seems only natural that the free CO_2 content would also be subject to fluctuation. Indeed, it is now known that this content of CO_2 in the alveolar air which changes, of course, with the free CO_2 content of the blood, is not as constant as it was formerly thought to be. Dodds[4] has recently demonstrated that following the intake of food there is at first a rise in the CO_2 tension of the alveolar air of 2 – 6 mm. followed later by a fall of a similar magnitude below the original level. Our determinations were done usually in the afternoon but irrespective of meals.

We have made use of the figure for the CO_2 content of air after equilibration in the rectum. The free CO_2 content of the blood was calculated from the figure as follows :—

The partial pressure or tension of CO_2 in the rectal air can be determined from the equation

$$\text{Tension} = \frac{\text{Percentage of } CO_2 \times (\text{Bar. press.} - \text{water vapour pressure})}{100}$$

If the barometric pressure be taken as 760 mm. Hg. and the water-vapour as 47 mm. Hg., the equation reads

$$\text{Tension} = \frac{\text{Percentage of } CO_2 \times 713}{100}$$

In order to determine the amount of CO_2 in the blood at this tension, use has been made of the coefficient of solubility of CO_2 in blood plasma which has been worked out by Bohr to be 0.54. This means that 1 c.c. of blood exposed to a pressure of 760 mm. Hg. of CO_2 will hold 0.54 c.c. of CO_2 at N.T.P. Accordingly it becomes easy to calculate the free CO_2 content of the blood from the following formula

$$\text{Free } CO_2 = 0.54 \times \frac{\text{Tension of } CO_2 \text{ in Rectal Air} \times 100}{760}$$

The total CO_2-combining power of the blood-plasma was determined by the method of Van Slyke. As we questioned the accuracy of the samples of true plasma, the plasma was in each case saturated with CO_2 at a tension of approximately 40 mm. Hg (the worker's own alveolar air). The difference

between the total CO_2 combining power and the free CO_2 we have taken to represent the combined CO_2.

It was thus possible to ascertain the *p*H of the blood by making use of the Hasselbalch formula, $pH = pK_1 + \log \frac{BHCO_3}{H_2CO_3}$ in which the Sorensen nomenclature is employed as shown in the following example. pK_1 is a constant and was taken as 6.1.

EXAMPLE :—

Percentage of CO_2 in rectal air = 5.5%

Tension of CO_2 in rectal air $\frac{5.5 \times 713}{100}$ = 39.2 mm.

Percentage of CO_2 in arterial blood $\frac{0.54 \times 39.2 \times 100}{760}$ = 2.79%

CO_2 combining power = 62.7%

Combined CO_2 (62.7 − 2.79) = 59.91%

$$pH = pK_1 + \log \frac{BHCO_3}{H_2CO_3}$$

$$= 6.1 + \log \frac{59.91}{2.79}$$

$$= 7.43$$

TABLE II.

Case No.	Name.	Age in years.	Mean CO_2 content of rectal air.	Tension of CO_2 in arterial blood.	Free CO_2 content of arterial blood.	Total CO_2 combining power.	Combined CO_2 content of blood plasma.	*p*H of the Blood.
1	W.F.	11	5·5	39·2	2·79	62·7	59·91	7·43
2	A.McL.	12	6·3	44·9	3·19	67·1	63·91	7·40
3	W.McC.	7	5·0	35·7	2·53	62·3	59·77	7·47
4	C.F.	10	5·0	35·7	2·53	61·3	58·77	7·47
			4·4	31·4	2·23	58·4	56·17	7·50
5	J.T.	6	7·0	49·9	3·55	71·9	68·35	7·38
6	W.McM.	4	5·3	37·8	2·69	52·6	49·91	7·37
			5·5	39·2	2·79	58·4	55·61	7·40
			6·8	48·5	3·45	64·0	60·55	7·34
			5·8	41·4	2·94	61·3	58·36	7·40
7	W.C.	9	6·8	48·5	3·45	61·0	57·55	7·32
			6·6	47·1	3·34	65·2	61·86	7·37
8	W.C.	6	4·2	30·0	2·13	49·7	47·57	7·45
9	S.K.	7	6·1	43·5	3·09	55·0	51·91	7·33
			5·9	42·1	2·99	57·4	54·41	7·36
10	V.McK.	7	6·4	45·6	3·24	63·2	59·96	7·37
			5·5	39·2	2·79	59·4	56·61	7·40

In Table II are shown the *p*H values worked out on cases taken indiscriminately in the wards. In no instance was the subject suffering from fever or any obvious disturbance of the acid-base balance. It will be seen that in this series of "normals" the variation in the *p*H values lies between 7.32 and 7.50. This agrees quite well with the findings of other investigators who have arrived at the *p*H by using Hasselbalch's formula. Peters, Barr and Rule[5] in normal controls (adults) found variations from 7.23 to 7.45 and Straub and Meier[6] from 7.30 to 7.42.

Several points of interest emerge from a consideration of the findings in our cases. In case 5 the tension of CO_2 in the rectal air was practically 50 mm. Hg. which in comparison with the usual normal alveolar air tension of 40 mm. Hg. seems much too high, but on estimating the CO_2-combining power, it was also found to be correspondingly high and the result was a normal *p*H value of 7.38. It is also noteworthy that in the second observation in Case 4 and in Case 8, where the tensions are both approximately 30 mm. Hg, the *p*H values as determined by this method are tending to alkalinity, namely 7.50 and 7.45. In addition the table serves to exemplify the extraordinary variations which occur in the CO_2 combining power (alkaline reserve) in cases which are presumably normal so far as their acid-base balance is concerned.

TABLE III.

No.	Name	Age Yrs.	Date.	Remarks.	Mean CO_2 Content of rectal air.	Tension Free of CO_2 in arterial blood. CO_2 in arterial blood.		Total CO_2 combining power.	Combined CO_2 content.	*p*H of the Blood.
1	W.C.	6	12/2/26	Ketogenic diet begun	5·6	39·9	2·84	57·4	54·56	7·38
			17/2/26	13/2/26, discontinued	4·4	31·4	2·23	37·1	34·87	7·29
			18/2/26	on 18/2/26.	4·3	30·7	2·18	42·9	40·72	7·37
			22/2/26		6·2	44·2	3·14	62·3	59·16	7·38
2	A.M.	9	27/2/26	Ketogenic diet begun	5·5	39·2	2·79	56·5	53·71	7·38
			5/3/26	28/2/26, discontinued	5·5	39·2	2·79	49·7	46·91	7·33
			7/3/26	on 5/3/26.	6·9	49·2	3·49	72·0	68·51	7·39
3	J.R.	2	10/1/26	$CaCl_2$ gr. XXX 6x	3·9	27·8	1·97	50·7	48·73	7·49
			14/1/26	begun on 11/1/26 and	4·9	34·9	2·48	50·7	48·22	7·39
			17/1/26	continued till 17/1/26	5·0	35·7	2·53	47·7	45·17	7·35
4	T.R.	8	4/1/26	Mild clinical acidosis.	5·0	35·7	2·53	38·1	35·57	7·25
			5/1/26		5·4	38·5	2·73	38·1	35·37	7·22
			6/1/26		6·0	42·8	3·04	62·3	59·26	7·39
			8/1/26		4·4	31·4	2·23	52·6	50·37	7·45
5	A.L.	12	19/2/26	Diabetes.	5·5	39·2	2·79	46·8	44·01	7·30
			25/2/26		6·4	45·6	3·24	62·3	59·06	7·36
			4/3/26		6·6	47·1	3·34	61·3	57·96	7·34

We have also investigated the change in the *p*H of the blood in children in whom a mild acidosis has been produced either by a ketogenic diet or by the administration of calcium chloride. Case 1 and 2 (Table III) show the influence

of a ketogenic diet. In Case I, the *p*H had already swung back before the diet was discontinued. This we believe to be correct as it is recognised by those who have carried out investigations with subjects on this diet that the acidosis tends to disappear very often as the subject becomes accustomed to the diet[7]. Case 3 appeared to be an ideal case in which to administer the acid therapy, because although the alkaline reserve was normal or even on the low side, the CO_2 tension of the rectal air was very low and the *p*H was therefore tending to the alkalotic side. On administration of calcium chloride 30 grains four-hourly, the *p*H fell from 7.49 to 7.39 and later to 7.35. The readings were obtained in Case 4 during the recovery from a mild clinical acidosis. In this case the *p*H value was 7.45 four days after admission, although on this occasion the lowest CO_2 tension in the rectal air was recorded. Case 5 is that of a diabetic admitted with a mild acidosis (acetone++) and in which two subsequent determinations were made when the acetone had disappeared from the urine.

It is of course a debatable point whether the air injected into the rectum equilibrates with arterial, capillary or venous blood, or with the tissue juices. The figures for the CO_2 tension are very similar to those found by Argyll-Campbell[2] in his experiments on rabbits with air injected subcutaneously or intra-peritoneally. He states that the tension of CO_2 in air injected under the skin or into the peritoneal cavity is the same as that in the alveolar air, which is usually believed to be in equilibration with the arterial blood.

It may be asserted that a direct determination of the *p*H by the hydrogen electrode or by a colorimetric method is more accurate. Such a method, however, only gives an indication of the reaction of the blood without throwing any light on the processes which the body brings into play to produce this reaction. Haldane[8] has stated that the animal organism tends to regulate the reaction of the blood in a much more delicate way than can be determined by even the finest chemical means. Hence, whether the figure obtained by this method represents arterial CO_2 tension or not, at any rate, when correlated with the total CO_2 combining power as shown above, the information obtained is of significance in two definite directions. First, it gives an indication of the state of the acid-base balance, whether tending to an acidosis or an alkalosis, and secondly, it throws some light on the mode of operation in the production of such a change, as well as showing compensated changes not recorded by a *p*H determination.

Conclusions.

1. An indirect method of determining the CO_2 tension of arterial blood in children by means of air injected into the rectum is described. The method unfortunately is inapplicable in children under two years of age.

2. A method of determination of the *p*H of the blood by means of Hasselbalch's formula is outlined and some results reported.

3. The *p*H of the blood calculated by this method varies in normal children over two years from 7.32 to 7.50.

We desire to express our gratitude to the Medical Research Council, by whom the expenses of this research were defrayed.

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SCIENCE AND THE BRITISH MEDICAL ASSOCIATION.

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SCAPHOCEPHALY, OXYCEPHALY AND HYPERTELORISM. With Reports of Cases.

BY

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The congenital abnormalities of the head, which have been described under the names of scaphocephaly, oxycephaly and hypertelorism, are sufficiently uncommon to justify the publication of such cases when they occur. The nomenclature of these conditions has been in a state of some confusion, and the work of Park and Powers[1] and Greig[2] [3] has been valuable as presenting a clear clinical and anatomical picture in each case.

Case I at 9 months.

The cases which are included in this study offer an opportunity of contrasting and comparing these deformities, and of considering whether the differences between them are not differences of degree rather than kind. Greig has pointed out that the most striking feature both of oxycephaly and hypertelorism, anatomically, is an abnormal shape of the sphenoid bone.

It is our intention to describe a case of scaphocephaly and a case of hereditary oxycephaly, and briefly to express our reasons for complete agreement with Greig on the question of the importance of the sphenoidal abnormality.

CASE 1. A. C., æt. 6. Female. Was brought to the Out-Patient Department of the East London Hospital for Children because of whooping cough and increasing shortness of breath. There was a history of a fortnight's illness, during which time the child had been getting steadily worse.

On examination, the curious shape of her head and the vacant, staring expression, combined with the extreme exophthalmos, gave her a most bizarre appearance. She was pale and obviously extremely ill. There was a broncho-pneumonia of the lower lobes of both lungs. No other abnormality was discovered, apart from webbing of the second and third toes of each foot.

The Head. The vault was high and the vertex was shaped like the keel of a ship, the forehead coming to a point resembling the bow, and the occiput being prominent posteriorly, simulating the stern. The highest point was in front of the anterior fontanelle, at the site of which there was a marked depression. The head was elongated antero-posteriorly, and narrowed laterally, as is shown in the photographs and by the following measurements :—

Nasion to external occipital protuberance, 13½″, the normal for that age being 12¼″.

The parietal eminences were absent, the bi-parietal measurement being 11″ against the normal 13″.

The circumference was 19½″, quite normal.

Case I at 9 months.

The face was narrowed, measuring 5″ from the root of one zygoma to that of the other, the normal being 6″.

The palate was highly arched, and only one molar tooth was present on either side.

On transillumination the maxillary antra appeared to be non-existent. Exophthalmos was extreme. There was no nystagmus or strabismus, and the pupils reacted to light. Mr. Davenport reported that the optic discs were normal. Hearing, taste and smell were normal as far as could be ascertained under the circumstances ; the child had a vacant expression and was very dirty in her habits, passing her dejecta under her. She appeared to live in a state of constant fear, crying out when approached, and it was decided that her mental state was due to chronic neglect and ill-treatment, rather than to actual mental deficiency.

Blood. There was a lymphocytosis, ascribable to the pertussis, nothing else abnormal.

Wassermann reaction. Not done.

Urine. Quite normal in every respect.

X-ray of Skull. Marked thinning of the bones of the vault. Digital markings seen. Flattened pituitary fossa, and marked under-development of both wings of the sphenoid. The appearances are those of deficient calcification. (Dr. B. Leggatt.)

Previous History. Full-term child—normal labour—is the youngest of four children, all healthy. The head condition is stated very definitely to have been present at birth. At the age of nine months she was taken to the Hospital for Sick Children, Great Ormond Street, because of the shape of the head. The following is the note of Dr. Donald Paterson, then Medical Registrar :—" Eyes protruding from the head like exophthalmic goitre. The back part of the head seems fairly round. The front portion has the appearance of having been pinched up in all directions—side to side—before backward. Child smiling—takes a great interest in surroundings, sits up and can stand if supported."

Family History. Mother had two miscarriages before the birth of this child.

Progress. She went rapidly downhill and died ten days after admission.

Post-mortem. (Dr. Temple Grey.) Done ten hours after death. The skull, on being opened, is seen to consist of the outer table only, and to be greatly thinned, being semi-transparent and in places actually deficient. There is complete absence of diploë. The skull is sutureless. The digital markings are well shown. The sphenoid was seen to be much smaller than normal, the superior orbital fissure being generally contracted to a gross degree. The orbital cavities were of normal shape, but were very small, being generally contracted. They contained a marked excess of fat. The frontal, maxillary and sphenoid regions contained no air-cells. The brain was normal, and shewed no evidence of atrophy. The lungs were the seat of an acute septic broncho-pneumonia. The kidneys, thymus and thyroid were normal. The webbing of the toes has already been mentioned.

Case 2. D. F., æt. 8½ months. Female. Was a full-term child. The presentation was transverse, but the delivery was normal. She is a bottle baby, and soon after birth had a " bad cough," with which she was very ill. She had whooping cough at two months and influenza at five months. She recovered well from all these illnesses and is now well and healthy, except for a small umbilical hernia. The deformity of the head was definitely present at birth.

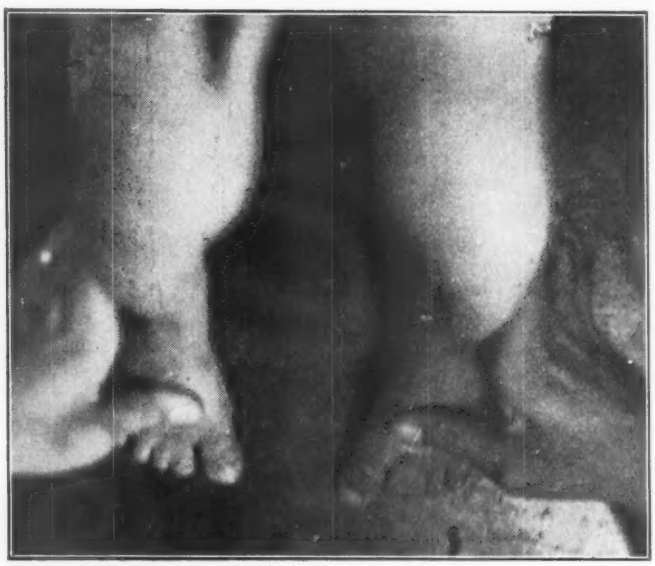
On examination, she is a plump, rosy-cheeked, healthy-looking child. The head is oxycephalic in shape, resembling rather the traditional helmets of the Roman legionaries. The cranial vault is high, the highest point being situated one inch behind the bregma. Behind this the head slopes gently away for three inches, then descends almost vertically to the external occipital protuberance, which is unobtrusive but can be identified. The parietal eminences appear to be absent, but there is bulging of the temporal regions on both sides, sufficient to hide the ears from view when the head is regarded from the front. There is no sign of either anterior or posterior fontanelle, and no sutures can be felt. The forehead ascends with a slightly forward inclination for 1½″, almost to the bregma. Its most prominent part is in the midline, from which it slopes away on either side, the frontal eminences being absent. The superciliary arches are very faintly defined, and above them on each side is a definite grooved depression. The bridge of the nose is broad and flattened to a greater extent than usual at this age, and this gives an appearance of " far-apartness " to the eyes, which are, however, no further apart than normal. The nasal bones are further deformed, the lower portions passing directly forwards at right angles to the upper parts. The face is triangular in shape, though this is partly disguised by the chubby cheeks. The palate is narrow and very highly arched and no teeth are present. The lower jaw is perhaps slightly prominent, though this is relative rather than actual. There is no exophthalmos. There is double internal strabismus but no nystagmus. The pupils are small, equal and concentric ; they react normally, and the optic discs are normal. There are no ocular palsies. The following measurements are of interest :—

Greatest circumference, 16″.
Nasion to external occipital protuberance, 9″.
Bi-parietal, 12″.
Bregma to symphisis menti, 7″.

There is a slight degree of webbing of the second and third toes of the left foot, which also shows a degree of talipes deformity. The left leg is half-an-inch shorter than the right. Joint movements are free and full in both upper and lower limbs. There is free extension at both elbows, but both give a slight click when full extension is insisted on. Sight and hearing by ordinary methods are normal. The child sits on its mother's knee, bright and lively, reaching out for things and turning her head to a sound, and takes a great interest in her surroundings. She does not stand yet, but the mother states that she has said " Dada " to her father.

X-ray of Skull. (D. F. and M. F.) Both skulls show exactly similar changes (Cases 2 and 3.)

In lateral view the skull appears abnormally thick, and there is no well-defined pituitary fossa. No digital markings are present. On antero-posterior view the head is slightly asymmetrical, and abnormal shadows are seen, due to the enlarged greater wings of the sphenoid. (Dr. B. Leggatt.)



Case I at 9 months.

CASE 3. Mrs. F. Aged 40. Is the mother of the previous case. Her birth was normal as far as she knows, but she was one month premature. She was a breast fed baby and has always been healthy. She worked as a dressmaker before her marriage, and still does fine sewing. She has never suffered from headaches at any time, even after reading, and does not wear glasses now. The deformity of the head was definitely present at birth.

On examination, she is a healthy-looking woman of normal stature. The head, though, of course, on a larger scale and with one or two minor differences, resembles the infant's head with ludicrous exactness. The slope of the head, the temporal bulging and the shape and inclination of the forenead are all faithfully presented. The most obvious difference is one which might be expected, and that is the nose. This is broad across the bridge itself, measuring a quarter of an inch across, but falls vertically to the level of the eyes on either side. The anterior nares are deep and roomy. The only other difference of note is the fact that the face is not markedly narrowed, and the palate is normal in shape. The teeth are absent, except one carious incisor. There is no exophthalmos or nystagmus, while there is a slight double internal strabismus, just as in the case of the child. The optic discs are normal. There are no other abnormalities of any kind, and the special senses are unimpaired. As stated above, she still does fine sewing.

She is quite up to the average in intelligence, and though garrulous is distinctly "all there." She states that when she was a dressmaker she was accustomed to take all her customers' measurements and write them down afterwards.

Family History. Her husband and his family are normal. A maternal cousin, female, has a similar deformity and is mentally deficient (unfortunately we had no opportunity of examining this patient). She has five children, four of whom are in every way normal. The youngest is our second case. There is nothing further of any interest.

In discussing these cases it is proposed to compare them one with another, rather than to regard them separately, and to consider any possible relationship they may have to hypertelorism. The bony abnormalities of the skull itself

Cases II and III.

will first be reviewed, the clinical side of the problem being dealt with later in the light of these.

The work of Greig on these conditions is classical, and those interested in the finer anatomical details are referred to his articles [2] [3].

A consideration of the radiological reports with, in the first case. the post-mortem findings, studied in conjunction with Greig's description of hypertelorism, shews that each of these deformities is associated with a definite developmental abnormality of the sphenoid bone. This sphenoidal abnormality was emphasised by Greig, who shewed also that it begins very early in development.

In the first case, one of scaphocephaly, the radiogram showed considerable under-development of the greater wings of the sphenoid, which was confirmed post-mortem. In the two cases of oxycephaly the greater wings were seen to be grossly enlarged. In hypertelorism, on the other hand, Greig found the lesser wings to be very much larger and more solid than normal, being as large as, or larger than, the greater wings.

In scaphocephaly and oxycephaly the relationship of the sphenoidal abnormality to the deformity is easily seen. In the scaphocephalic skull the poor development of the greater wings of the sphenoid, by partially removing their " scaffolding " function, necessarily brings about a narrowing of the whole skull, especially the anterior part. This narrowing has two secondary effects, namely, the elongation which has been noted, and the degree of elevation of the vault, with absence of frontal and parietal eminences. The generally small size of the orbits, which are not relatively shallow, is also due to the abnormal development of the sphenoid. The greater wing of the sphenoid forms the posterior part of the lateral wall of the orbit, and the under-development of this important structure, with consequent general narrowing of the skull, brings about the generally contracted condition of the orbit found at autopsy. One would not expect to find any relative shallowness of the orbit in this case.

In the cases of oxycephaly the shape of the skull is brought about in the same way, although the difference in the shape of the sphenoid brings about an altogether different deformity. Here the abnormally large solid greater sphenoidal wings push the temporal bones laterally, leading to temporal bulging, with an increase in the transverse diameter of the skull at this point, and wide, shallow orbits. The skull must of necessity adapt itself to this, and the occiput comes forward, cramping the base of the skull, as is seen by the crowding of the foramina in this region, and shortening the antero-posterior diameter. Thus the skull is broader and shorter than normal. The natural consequence of this state of affairs is the great increase of the height of the cranial vault, which has given the condition its name, and the flattening of the occipital region.

Other features of these two types of skull, for instance, the maldevelopment of the maxillæ, which causes the highly arched palate, the thinness of the skull bones with absence of diploë, and the digital markings so frequently met with, shew that other factors are present ; but the fundamental fact is the abnormal development of the sphenoid. One further point must be mentioned. Both these deformities are associated with *total absence of sutures ;* " where the bones touch they fuse," as Greig has said.

On turning to hypertelorism, the relationship is less evident, and at first sight appears doubtful. The skull is not sutureless, though the sutures are incomplete, and do not form digitations ; and a number of inter-sutural bones are present, internasal, parieto-mastoid and pterionic. It is desired, however, to focus attention on the sphenoid, and consider how the abnormality there affects the problem. The lesser wing of the sphenoid forms the posterior part of the roof of the orbit, and its anterior border articulates

with the orbital plate of the frontal bone. It will be seen that an enlargement of this wing, so gross as in the case in hypertelorism, will push the whole frontal bone upwards, forwards, and outwards, and with it the corresponding maxilla. The nasal bone of that side, which articulates laterally with the frontal process of the maxilla, is naturally involved in this displacement of the entire corresponding side of the face. It is thus easy to understand the necessity for an internasal bone and the retroussé character of the nasal bones themselves. The interfrontal groove noted by Greig is readily accounted for in the same way, while the tilting of the frontal bone which must necessarily occur explains the combination of the low forehead with slight prominence of the frontal eminences.

Cases II and III.

On these grounds is based the contention that the " far-apartness " of the eyes and divergence of the orbital axes, the two most distinctive features of hypertelorism, are directly due to the overdevelopment of the lesser wings of the sphenoid.

This review of the problem, brief as it is, suffices, it is believed, to shew that the origin of these deformities, though they differ in many ways, is the same, namely, abnormal development of the sphenoid bone.

The clinical side of the question will now be considered.

Of associated deformities, symmetrical and otherwise, on which so much stress has been laid, little will be said. This is not because their great importance

is not appreciated, but because the exhaustive treatise of Park and Powers leaves nothing to say. It is merely desired to point out that similar deformities occur in both scaphocephaly and oxycephaly, and in considering the absence of such deformities in cases of hypertelorism so far reported, to refer to a case which was shown to the Royal Society of Medicine by Dr. Robert Hutchison in 1910. This case is referred to by Greig, who gives it as his opinion that, though shown as a case of oxycephaly, it is in reality a case of hypertelorism. On examining the report of the case, and studying the photograph, the case appeared to us to partake of the characters both of oxycephaly and hypertelorism. The head is said to have been oxycephalic, though the photograph gives no confirmation of this, being a " full-face " view. The frontal eminences are definitely absent, and the superciliary arches are ill-defined. There is no temporal bulging to be seen, however, the nose is remarkably broad and flattened, and there is obvious " far-apartness " of the eyes. Other points of resemblance to hypertelorism are the presence of an interfrontal groove, a divergent squint and, what is well shown in the photograph, subcutaneous thickening. In association with the cranial deformity there was syndactyly with " irregularly arranged toes." This is a case which seems to form a link between oxycephaly and hypertelorism, in association with which were deformities of the limbs. The presence of deformities in these cases is, however, inconstant, and it is felt that their absence in hypertelorism does not in any event invalidate the hypothesis proposed.

It is surprising that instances of a familial history in these cases are so uncommon. In explanation of this we quote Greig :—" In oxycephaly as a congenital defect heredity ought to occur, but examples are restricted since those but slightly affected do not seek medical advice and those grossly affected are not acceptable in marriage."

Our second and third cases, however, provide an example of a definitely hereditary abnormality of cranial development. The mother's cousin was similarly affected, and in addition was mentally defective. This is emphasised, as it lifts these conditions out of the " freak " class, and gives them a position of great practical importance.

Slight mental deficiency, which occurs in most cases of malformation of the skull, is merely a natural effect of the very early developmental abnormality of the skull on the growing brain, and is fully discussed by Greig. The other clinical characteristics are all secondary to the cranio-facial deformity or to one another. Little, therefore, can be argued from their occurrence or non-occurrence in a particular case. For instance, the exophthalmos is due to the inadequate accommodation provided by the orbital cavities for the eyeballs in the majority of cases of oxycephaly and scaphocephaly. In Cases II and III there was no exophthalmos. This means simply that the orbits were not as shallow as usual, and therefore the eyeballs could be accommodated comfortably, and by no means invalidates the diagnosis. Nystagmus is common, and

is secondary it is believed to the exophthalmos when present, being produced in the same way as miners' nystagmus. Optic atrophy is another common concomitant of all these conditions, but like exophthalmos depends on the degree of deformity of the orbit and optic foramen.

Conclusion.

Scaphocephaly, oxycephaly and hypertelorism are believed to bear a definite relationship to one another, and this relationship consists in a common origin ; namely, an abnormal development of the sphenoid bone.

The association of mongolian characteristics with hypertelorism noted by Greig, Cockayne and Braithwaite[5] appears to be of great importance, though its significance cannot be assessed. The occurrence of epilepsy in a case of Cockayne's[6] may be mentioned in this connection.

No résumé of the literature has been attempted, but we desire to acknowledge our debt to the following authors, whose work we have studied, in addition to those mentioned in the text :—H. Morley Fletcher[7] [8], R. C. Jewesbury and J. C. Spence[9], H. C. Cameron[10] and Dr. C. Muir[11].

We wish to thank the Honorary Staff of the East London Hospital for Children for permission to publish the first case. The other two cases were kindly sent to us for investigation by Dr. Donald Paterson, whom we desire to thank for his encouraging advice and criticism. To Dr. Sheldon we are indebted for access to the notes, and for the photographs of Case I while at the Hospital for Sick Children, Great Ormond Street.

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OBSERVATIONS ON THE MANIFESTATIONS OF RICKETS IN LIVERPOOL.

BY

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It has been said that certain manifestations of rickets are more frequently seen in some districts than in others. One would be inclined to think that this might be accounted for by the keenness of individual clinicians to elicit a particular sign were it not for the fact that there is a certain measure of agreement between the physicians in different towns and countries as to the relative frequency of certain manifestations of the disease in particular districts. What accounts for this peculiar geographical localization of certain signs and symptoms of this disease is a matter of conjecture.

Incidence of Rickets in Liverpool.—Only within recent years has the extreme prevalence of rickets been realized. Osler pointed out that the incidence of pernicious anæmia in any district depended on the acuity of the local observers; similarly the records of the prevalence of rickets in any country depend on the acuity and experience of the observers. Clinicians adopt widely divergent standards of diagnosis, some diagnosing rickets when an infant has sweating of the head, flabby muscles, a protuberant abdomen and delayed dentition, while others maintain that the radiological evidence of bone changes alone is reliable. The bone changes at the wrist that can be shown radiologically are not the earliest pathological changes of rickets. The disease may be present at the end of the sixth week of life. With the technique at present attained in radiological photography it is not possible to show the detail needed for diagnosing early rachitic changes in the cranial bones or in the costo-chondral junctions in which the earliest bony changes occur.

The British workers in Vienna[1] have shown conclusively that very slight enlargement of the costo-chondral junctions is indicative of rickets, but it would be as absurd to label as rachitic every infant with beading of the ribs as it would be to diagnose anæmia in every infant whose hæmaglobin was below 100%, or to class as tuberculous every patient who gave a positive Von Pirquet test.

In Liverpool almost all infants of the hospital class between the ages of 6 and 18 months on careful examination show unmistakable clinical signs of early rickets, if one includes beading of the ribs, which is undoubtedly an early sign. It is exceptional to find a patient of this class wholly free from the disease.

Breast-feeding and Rickets.—It is commonly thought that breast-feeding prevents the onset of rickets. This belief is illusory, for although breast-fed infants are less prone to suffer from the severer manifestations of the disease during the first year of life, yet they are not wholly immune. That the disease may be well established even at an early age in a breast-fed infant is shown by the following case.

T.D. Male. Age 6 weeks. Breast-fed infant. Admitted as marasmus but died a couple of days later from broncho-pneumonia. There was definite beading of the costo-chondral junctions, but the epiphyses at the wrists were not noticeably enlarged. Sections of the former showed marked rickets, while sections through the distal epiphysis of the radius showed that the disease was present but was not so far advanced.

Comparatively few breast-fed infants are admitted to Alder Hey Hospital, but of them the majority show unmistakable clinical evidence of slight rickets.

Hess[2] states that although breast-feeding protects to some extent against rickets it does not prevent it. Among the Russian-Jewish population in the tenement district of New York he found that 40% of the breast-fed infants showed radiological evidence of rickets. In reality the incidence of the disease must have been much greater. He notes that the babies were a particularly well-nourished group and that the diets of the mothers were liberal, containing an abundance of fat.

A fact that does not seem to have been emphasized in the literature is that although breast-feeding diminishes the severity of the disease during the first year of life, it exerts absolutely no preventive action against the development of rickets in the following years. An inquiry into the histories of twenty-five patients between the ages of eighteen months and four years who showed radiological evidence of severe and active rickets elicited the surprising fact that 76% had been wholly breast-fed for three months or longer. An analysis of the figures showed that 20% were breast-fed for more than three months but less than six months, 32% were breast-fed for nine months, while 24% were breast-fed for over a year.

To ascertain the proportion of infants in Liverpool that are breast-fed for three months or longer I examined the records of four hundred healthy infants who had been brought to infant welfare centres. It was found that 65% were wholly breast-fed for three months or longer. There was, however, reason to believe that the true proportion of breast-fed infants was less than this figure. I am unable to account for the large proportion of rachitic infants in whom a history of breast-feeding was obtained, unless it be that among patients of the hospital class there is a small proportion of women who are so poor that they have no choice but to breast-feed their infants. Women living in such dire poverty are unable to provide suitable hygienic surroundings for their infants, who are thus more prone to suffer from rickets.

Craniotabes.—In Vienna[1] a third of all rachitic infants suffered from craniotabes. Hess[2] states that craniotabes is regarded by many clinicians as one of the earliest and most reliable signs of rickets and that it is present in 10% of infants (presumably in New York) at the age of six months.

De Buys[3] working in New Orleans states that 60% of infants born in the winter months suffer from craniotabes at the age of four months. In Liverpool craniotabes must be a very rare manifestation of rickets; I have examined a hundred rachitic infants and carefully searched for this condition but have failed to detect a single example. Nor have I ever noted an instance of this condition among the many hundred rachitic infants I have seen. Inquiries from my colleagues in this hospital have elicited the answers that they have never seen a case.

Sweating.—Sweating is stated in many textbooks to be one of the earliest symptoms of active rickets. The rachitic infant's brow is said to be bathed in perspiration, the pillow-slip bearing the moist imprint of the baby's head. I have carefully examined many rachitic infants in hospital, both young infants who showed the early signs of rickets and older children who showed well-marked radiological evidence of active rickets, and can state dogmatically that these patients, while in hospital at least, do not perspire. The brows of a few may be moist, but profuse sweating does not occur. Going through an infants' ward recently I noticed a baby who was perspiring freely about the head; this patient was being treated for bronchitis and malnutrition, and on examination I failed to detect any definite evidence of rickets. In Vienna[1] sweating is a rare symptom. Both Hess[2] and Mackay[4] state that sweating cannot be regarded as pathognomonic of rickets.

Nervous Complications.—Some authorities emphasize the nervous complications of rickets. Tetany is stated to be a complication of rickets frequently seen in Glasgow. During the eighteen months that I have paid special attention to the study of rickets in Liverpool I have seen only two cases of tetany and these occurred in children who showed no signs of severe rickets. I have not seen a case of laryngismus stridulus in eighteen months at Alder Hey. Although cases of convulsions are common, they do not occur in patients suffering from severe rickets.

Marasmus and Rickets.—It has been stated that marasmus and rickets are rarely found together. Marasmus is an indefinite term and as commonly used connotes a variety of different conditions. In infants diagnosed as marasmic I have frequently found clinical evidence of early rickets and on several occasions have confirmed the diagnosis by histological examination of the costo-chondral junctions after death, as in the case mentioned earlier in this article. Hess[2] has pointed out that the manifestations of rickets are most marked during active growth and that any illness that retards growth tends to cure the rachitic condition.

Catarrhal Complications.—It is commonly stated that rickets predisposes to bronchial and intestinal catarrh and there seems to be some experimental evidence to support this view[5]. Owing to the well-nigh universal incidence of slight rickets among infants and young children of the hospital class it is hard to formulate a reasoned judgment on the subject. I can present no

figures, but I have formed a very definite clinical impression that patients with radiological evidence of active rickets are not more prone to develop catarrhal complications than are other children in the same wards.

Osseous Lesions.—In Newhaven[6] in America 90% of infants under six months of age are said to show radiological evidence of rickets. My experience in Liverpool has been that there is usually little or no evidence of rickets in radiograms of the wrist before the end of the first year. In a few cases some fuzziness at the distal end of the ulna may be apparent, but in the majority of cases there is no definite evidence of rickets in the radiograms of infants under a year even in the presence of active clinical rickets. Why the disease in Newhaven should produce such early osseous lesions is not easily explained, unless it is merely due to a different standard of interpretation of radiograms. In my work I have not regarded a slight degree of osteoporosis or splaying of the distal end of the radius as pathognomonic of rickets.

Tenderness of the Limbs.—Tenderness of the limbs in florid rickets is a point emphasized by the older writers. I have never been able to satisfy myself that this is a characteristic sign of rickets. After one has overcome a child's initial nervousness the rachitic patient does not appear to resent being handled. Certainly in older children who radiologically show acute rickets, tenderness is not usually present. Probably the belief that tenderness of the limbs is characteristic of rickets is a survival of the days before the clear differentiation between rickets and scurvy.

The Radiological Cure and the Clinical Cure.—Mellanby[7] has shown that in animals radiograms of the bones is a true criterion of the degree of severity of rickets. In children the healing process may be visualised in a series of radiograms of the wrist taken at frequent intervals and the curative value of any specific therapy may so be appraised. It is probably correct to state that radiograms of the wrist give a true picture of the disease ; without them it is impossible to judge whether the disease is active, healing or cured.

The radiological cure of the disease does not always synchronize with the clinical cure. The radiogram may show calcification and definition of the bones, but the big square head, the beading of the ribs and the deformities of the lower limbs may persist for many months.

J.T. Age 2. The radiogram taken on admission showed severe and active rickets. Very marked genu varum was present. After nine months' treatment with cod liver oil, anti-rachitic diet and irradiations with an open-flamed tungsten-molybdino-cored carbon-arc lamp, a radiogram showed calcification of the bones at the wrist. The bowing of the legs persisted, in spite of daily massage, moulding and recumbency, and was almost unaltered four months after the radiological cure.

Contrasted with the older methods of treatment the newer methods produce very rapid calcification of rachitic bones. Elsewhere I have described[8] the rapid calcification produced by the oral administration of irradiated cholesterol. It seems doubtful whether in the treatment of patients suffering from marked deformities it is advisable to employ methods of

treatment that result in very rapid calcification of bones, which must retard the tendency to natural cure, decrease the curative value of massage and daily moulding of the part and render more frequent the need for osteotomy.

I wish to thank Dr. P. MacDiarmid, M.D., O.B.E., Medical Superintendent of Alder Hey Hospital, for his kindness in permitting me to mention these cases.

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A SUBSTITUTE FOR BUTTERMILK IN THE TREATMENT OF DIGESTIVE DISORDERS DURING INFANCY

BY

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In the treatment of digestive disturbances in infancy, especially in acute gastro-enteritis, acid milk mixtures have been used with success for some considerable time. Buttermilk was first used empirically in Holland, with very good effect, and was then adopted elsewhere abroad. At the present time the use of buttermilk, Finkelstein's *Eiweissmilch*, or concentrated protein milk, can be regarded as the usual routine treatment in acute gastro-enteritis, both on the continent and in America. Protein milk mixtures are, of course, acid milks, consisting of cow's milk curds mixed with buttermilk, or with equal parts of buttermilk and water.

Faber [1] and Levine [2] have both recently written excellent reviews concerning acid milk mixtures and their use in infant feeding. It is, however, still impossible to give an exact reason why such mixtures prove beneficial. Marriott and Davidson [3] believe that the reduction of the buffer value of the milk itself, which is brought about in acid milks, is chiefly responsible for their good effect, as it allows gastric digestion to be accomplished more easily. Since the secretion of hydrochloric acid in the stomach is decreased in infants suffering from gastro-intestinal disturbances, this is obviously a point of importance. Schiff and Mosse [4], however, doubt this explanation of the efficacy of these mixtures, and after an exhaustive and critical review of all the data, together with the results of their own experiments, frankly confess that they are unable to assign any one particular reason for their good effect. Györgi suggested that perhaps the lactate ion itself might be the responsible factor in the case of milks soured by lactic acid, but Brahdy [5] has been unable to find evidence of this.

It is possible that in the percentage composition of the mixtures themselves lies the explanation of their value. It has, however been generally considered that sweet milk mixtures of similar percentage composition do not achieve such good results.

If it be conceded that an acid milk mixture of the type above referred to is the food of choice in gastro-enteritis or in digestive disturbances, then it is a matter of importance, especially in hospital out-patient practice, to be able to employ a mixture of this sort which is easy of preparation or readily obtained, and which is cheap.

Discussion of a Buttermilk Substitute.—Fresh buttermilk itself is not easily obtained in this country. Its preparation by skimming or centrifuging cow's milk and subsequently inoculating this with Bacillus Bulgaricus, is not usually feasible in out-patient practice, any more than is the preparation of

protein milk. In any case, neither of these preparations can be arranged for by the out-patient mother herself. There exist dried powder preparations of both protein milk and buttermilk, but although this facilitates matters, the expense of such proprietary preparations puts them beyond the scope of the class with which we are dealing.

There is left the possibility of using ordinary skimmed cow's milk to which lactic acid has been added, such as is employed in cases of acute gastro-enteritis by Marriott. Although this may be properly prepared in certain cases, it presents difficulties in the majority of homes in this country, where ice is an unknown luxury. That is to say, the acid is poured into milk insufficiently cooled, and the formation of large tough curds results. In addition to this objection, the milk itself, unless kept properly covered and coming from a reliable source, will only be contaminated and augment the existing enteritis.

To get over these difficulties it was thought that skimmed milk powder prepared by the addition of water to which lactic acid (B.P. 75 per cent.), had been previously added, would effectually achieve the desired results. The milk powder is cheap, relatively sterile, and the addition of lactic acid to the water necessary to reconstitute such a milk so easy as to be virtually fool-proof. Numerous experiments have shown that the lactic acid in the proportion of a drachm to the pint (0·7 per cent.) can be added to the water required for admixture with the milk powder, and this brought to the boil and poured on the milk powder while stirring, without causing any more than the finest flocculent curd, all of which will easily pass through the teat of a bottle. It has also been found that no further clotting takes place in this mixture on the addition of rennin.

I first used this type of preparation in 1925 and subsequently Dr. Hamilton* has employed it in certain cases of digestive disorder with success. Powers [6] has recently stated that he has used a similar mixture in cases of acute gastro-enteritis with beneficial results.

Properties of the Acid Dried Skimmed Milk Mixture.—If a preparation so cheap and so easy to prepare has properties similar to buttermilk, there can be no reason why it should not be employed under similar conditions.

The percentage composition of buttermilk varies to a slight extent, but the following two analyses may be taken as representative :

	Veith (quoted by Thomson[7])	Finkelstein[8]
Protein...	3·6%	2·6%
Fat	0·5%	0·75%
Lactose	4·6%	3·25%

* Personal communication from Dr. C. K. J. Hamilton.

We may average these figures and take the following as the percentage composition :—

Protein	3·2%
Fat	0·6%
Lactose	3·9%

The salt content may be regarded as 0·75 per cent., and the calory value is equal to ten calories per ounce.

Two well-known firms provide skimmed milk powders, which when reconstituted by the addition of water in the proportion of one part of powder to ten parts of water have, according to their analyses, the following percentage compositions :—

	A	B	Average.
Protein	3·5%	3·3%	3·4%
Fat	0·1%	0·07%	0·08%
Lactose	5·2%	4·5%	4·8%
Ash	0·8%	0·7%	0·75%

The calory value of these is equal to approximately 10 calories per ounce.

If, as is the almost universal rule, the mother measures out the feeds by means of a teaspoon, a slightly different percentage composition will result. It has been found experimentally that two level teaspoonfuls of skimmed milk powder are of such weight that when added to an ounce of water a dilution of one part of powder to nine parts of water will result. This makes a ten per cent. increase in the above figures. Taking this into account, the difference in round numbers to be noted between the percentage composition of buttermilk and skimmed milk powder, is that the latter contains 1·5 per cent. more lactose and 0·5 per cent. less fat.

In the treatment of acute gastro-enteritis the lower fat content can be looked upon as an advantage. The slightly increased percentage of lactose present cannot be regarded as seriously disadvantageous. In the first place, the addition of 1½–3 per cent. of carbohydrate is nearly always prescribed with buttermilk itself, when it is employed. Secondly, the lactose content of the skimmed milk powder is less than 1 per cent. higher than the lactose content of breast milk which, when skimmed, is above all others, the food of choice in acute gastro-enteritis. There seems no good evidence that lactose itself in the amount present is liable to cause any harm.

The hydrogen ion concentration and buffer value of this mixture are the two other properties calling for description, and comparison with those of buttermilk.

Experiments to Determine the Hydrogen Ion Concentration and Buffer Value of these Preparations —In order to compare these properties in the case of buttermilk and the acid dried skimmed milk, determinations of the hydrogen ion concentration and titration curves were carried out with both.

Dried skimmed milk was made up in the usual way by the addition of water, to which, however, lactic acid had been added in the proportion of

0·7 per cent. of the mixture. This was centrifuged, and 5 c.c. of the supernatant fluid was pipetted off, placed in collodion sacs and dialysed against 0·85 per cent. CO_2-free saline. The hydrogen ion concentration of the dialysate was estimated colorimetrically by Gillespie's method[9] [10]. For comparative work this method is as accurate as desired. Whether the skimmed milk was made up in the proportion of one part of powder to ten parts of water, or in the proportion of one part powder to nine of water (two level teaspoonsful to the ounce), no apparent difference in the hydrogen ion concentration resulted, and therefore the readings obtained in these two dilutions have been considered together. In a series of fourteen experiments carried out with the above mixture, the following results were obtained:

In 1 expt., H.-ion concentration was equal to *p*H 4·4
,, 6 ,, ,, ,, ,, ,, ,, *p*H 4·6
,, 4 ,, ,, ,, ,, ,, ,, *p*H 4·7
,, 2 ,, ,, ,, ,, ,, ,, *p*H 4·8
,, 1 ,, ,, ,, ,, ,, ,, *p*H 5·0

Excluding the two extreme values, an average *p*H of 4·7 was obtained in twelve experiments. The figures were remarkably constant and in no case did the duplicate estimates vary by more than 0·1, and in the majority of experiments they were identical.

For comparison, similar experiments were carried out with fresh buttermilk and centrifuged cow's milk soured by the addition of *Bacillus Bulgaricus*. The hydrogen ion concentration of both these preparations proved to be similar, and the results are therefore considered together. The average reading of five experiments gave a value of *p*H 4·5, the extreme values differing by 0·2 *p*H.

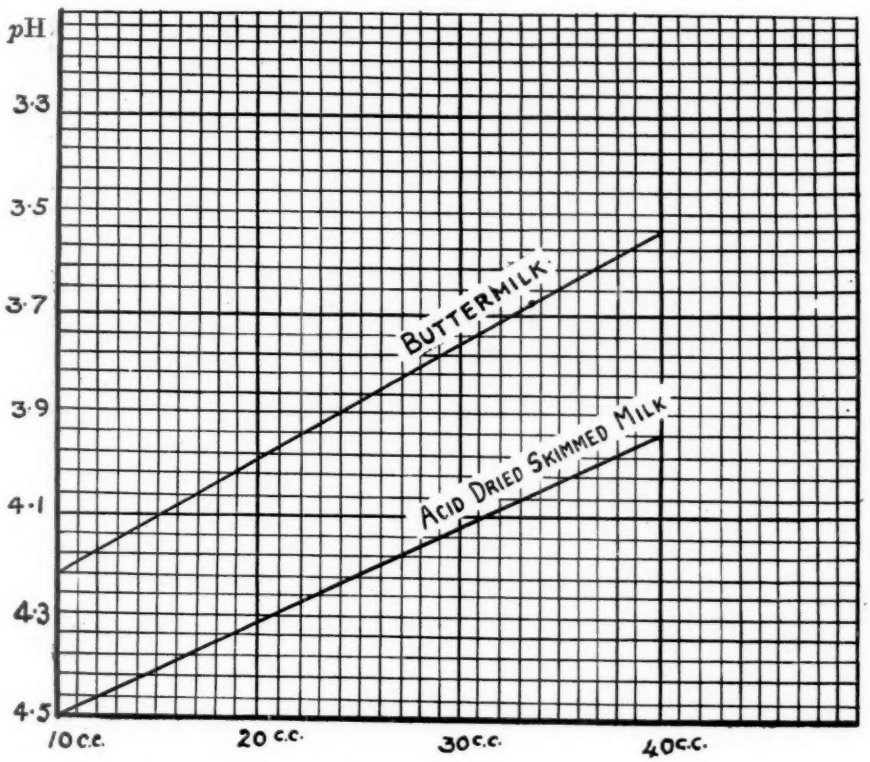
From the above experiments it appears that the hydrogen ion concentration of buttermilk, and of the mixture of lactic acid dried skimmed milk are for practical purposes the same.

In order to investigate the buffer value, titration curves were carried out and the results are given below:

	N/10 HCl. per 100 c.c. Milk Mixture.			
Skimmed dried Milk	plus 10 c.c.	20 c.c.	30 c.c.	40 c.c.
Expt. I	*p*H 4·5	*p*H 4·3	*p*H 4·1	*p*H 4·0
,, II	*p*H 4·5	*p*H 4·3	*p*H 4·1	*p*H 3·9
,, III	*p*H 4·5	*p*H 4·4	*p*H 4·1	*p*H 3·9
,, IV	*p*H 4·5	*p*H 4·3	*p*H 4·1	*p*H 4·0
,, V	*p*H 4·5	*p*H 4·3	*p*H 4·1	*p*H 3·9
Buttermilk	plus 10 c.c.	20 c.c.	30 c.c.	40 c.c.
Expt. I	*p*H 4·1	*p*H 3·9	*p*H 3·7	*p*H 3·5
,, II	*p*H 4·3	*p*H 4·0	*p*H 3·7	*p*H 3 5
,, III	*p*H 4·2	*p*H 4·1	*p*H 3·9	*p*H 3 7
,, IV	*p*H 4·2	*p*H 3·9	*p*H 3·7	*p*H 3·5

Figure 1 shows these results in the form of a graph made by averaging the results of all the experiments in each series. It will be observed that although the readings obtained in experiments with buttermilk are slightly more acid than is the case when the acid-dried skimmed milk mixture was investigated, the buffer values in both sets of curves are approximately the same.

Fig. 1.



N/10 HCl. per 100 c.c. of Milk Mixture.

The results as portrayed above will be seen to run practically parallel in the two series.

Summary and Conclusions.—The use of an acid dried skimmed milk mixture as a substitute for buttermilk is discussed. The preparation of the acid dried milk mixture suggested can easily be carried out in the poorest home and by the least intelligent person. Lactic acid in the proportion of 0·7 per cent. (one drachm to the pint) is added to the amount of water requisite for reconstituting the milk powder. This is brought to the boil and then mixed directly with the powder, stirring the while. A fine flocculent curd results, in which it is found no clotting takes place on the addition of rennin.

The percentage composition of this mixture differs little from that of buttermilk itself, and is suitable for use in cases of gastro-intestinal disturbance and acute gastro-enteritis.

A series of experiments has been carried out and shows that the hydrogen ion concentration and buffer values of this preparation are similar to those of buttermilk.

This acid dried skimmed milk mixture is therefore recommended as being suitable for use in all those cases in which buttermilk itself has proved of value, and can, in fact, be regarded as a suitable and efficient substitute.

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The Dick Test in relation to the presence of the Streptococcus Haemolyticus in the Throats of Individuals not suffering from Scarlet Fever

BY

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It is generally held by most authorities that when the throat of a Schick-positive reactor becomes infected with a strain of virulent *C. diphtheriæ*, the individual will almost certainly develop clinical diphtheria within a few days, and that when a Schick-positive reactor is found to be a carrier then the diphtheria organism is non-virulent.

It was resolved, therefore, to ascertain whether *S. hæmolyticus* could be found in the throat cultures of those who were Dick positive, and further to determine whether the various strains could be separated into scarlatinal and non-scarlatinal types. As it has already been shown (Smith, 1926, 1927, Griffith, 1926, James, 1926) that scarlatinal types cannot be distinguished by agglutination and agglutinin-absorption tests from strains of hæmolytic streptococci occurring in other infections, the various strains were tested for their power to produce a true exotoxin, and tests were made to determine if the exotoxins were neutralised by scarlatinal horse-antitoxin.

Methods.

The Dick test was applied in the first instance to seven nurses and thirteen patients in a scarlet infected children's ward, and secondly to forty patients convalescing from diphtheria, and at the same time swabs were obtained of the secretions of the throat. These secretions were emulsified in broth, and blood agar plates were inoculated and incubated overnight. Typical colonies were selected and replated. After an incubation period of twenty-four hours colonies were picked into tubes containing blood broth and incubated. The hæmolytic activity of each strain was tested by growing in twenty per cent. horse serum broth medium, and after an incubation period of eight hours 0·1 c.c. of the culture fluid was added to 1 c.c. of two per cent. washed sheep's red blood cells, and this mixture was incubated in a water bath at 37°C. for one hour. The various strains were also tested for their resistance to bile, and for their action in media containing the carbohydrates, lactose, salicin, mannite, inulin, and raffinose. The serological classification of these various strains was accomplished by methods already described (Smith, 1926, 1927).

For the production of toxin, flasks containing 50 c.c. quantities of Hartley's trypsin-broth were inoculated with the various strains. After an incubation

period of forty-eight hours 0·4 per cent. phenol was added to the cultures, which were then centrifuged. The supernatant fluids were passed through sterilised L2 Chamberland candle filters and the filtrates were stored in the refrigerator until required.

In order to test whether a filtrate contained a true exotoxin six intracutaneous tests (three on the flexor aspect of both arms) were made on a series of individuals with 0·2 c.c. of the following fluids :—

1. Dick test toxin=1 skin test dose.
2. Dick test control.
3. Toxin from strain under examination diluted 1 in 100.
4. Toxin from strain under examination diluted to 1 in 100 and boiled for four hours—control for test No. 3.
5. Toxin from strain under examination diluted to 1 in 100 with a concentrated horse scarlet fever antitoxin diluted 1 in 10. (This mixture was incubated in the water bath for one hour at 37°C. just prior to inoculation.)
6. Horse scarlet fever antitoxin diluted 1 in 10—control for test No. 5.

The scarlet fever antitoxin used in the neutralization test was certified as being capable of neutralising 50,000 skin test doses of toxin per c.c. so that 1 c.c. diluted 1 in 10 with salt solution would be capable of neutralizing 5,000 skin test doses of toxin.

Owing to the presence of horse serum in the neutralisation test mixtures a considerable number of 'pseudo' reactions appeared and these made the interpretation of skin tests difficult. All reactions which were complicated by the 'pseudo' factor, whether due to horse serum or due to protein in the toxin filtrate, were discarded, and only the clear cut results obtained twenty-four hours after making the tests have been recorded in the following pages. The reactions produced by the toxins are recorded as being +, ++, +++, ++++, and negative.

Results.

In a series of sixty cases twenty-seven gave a positive Dick test, and twenty-three a negative test. The relationship of the Dick tests to those harbouring *S. hæmolyticus* is given in Table I from which it will be seen that while eight cases harbouring *S. hæmolyticus* gave a negative Dick test, six cases gave a comparatively feeble positive reaction varying between one + and two ++. The serological classification showed that one Type I, two Type II, two Type X, and one unclassified strain were obtained from the Dick-negative reactors, and that one Type II, one Type III, one Type IV, two Type X and one unclassified strain were obtained from Dick-positive patients. In previous papers it has been shown that strains with the same serological characteristics were obtained from the throats of acute cases of scarlet fever.

TABLE I.

CASES SHOWING S. HÆMOLYTICUS.

Case No.	Age.	Dick Test.		Culture from Throat.	Serological Type.	Strain No.
		Test.	Control.			
2	22	0	0	+	I	1
4	22	0	0	+	X	2
11	21	0	0	+	II	3
18	4/12	0	0	+	II	4
19	1 3/12	++	0	+	II	5
20	5/12	0	0	+	II	6
23	14	0	0	+	X	7
25	3	+	0	+	X	8
35	5	++	0	+	IV	9
37	13	+	0	+	Unclassified	10
39	5	0	0	+	Unclassified	11
47	19	+	0	+	X	12
57	39	+	0	+	III	13
58	22	0	0	+	X	14

The results obtained on testing the filtrates for toxicity and for neutralisation with antitoxin are summarised in Table II. It was found, therefore, that all strains produced filtrates capable of giving reactions in human beings similar to the Dick test toxin. It was found, also, that the substance producing the reaction was destroyed by boiling for four hours and was neutralised by horse scarlet antitoxin. The majority of the strains produced a filtrate which, when used in a dilution of 1 in 100, caused many more positive reactions than the Dick test toxin. This was due to the fact that 0·2 c.c. of 1 in 100 dilution of a filtrate probably contained five to ten skin test doess instead of one skin test dose, and it can be shown that many more individuals react to five or ten skin test doses than to one skin test dose. So far as these tests go, there is nothing to indicate that the various toxins differ in constitution from the Dick test toxin, despite the fact that the toxins were obtained from strains belonging to five serological types and from two unclassified strains.

It has been established, therefore, that certain individuals, who are Dick negative or who give slight Dick-positive reactions, can be carriers of hæmolytic streptococci capable of producing a true exotoxin which can be neutralised by a horse scarlet fever antitoxin. This may indicate that those individuals who give feeble positive Dick tests and who harbour hæmolytic

TABLE II.

DICK TESTS AND TESTS WITH FILTRATES FROM STRAINS.

Series.	Case No.	Dick Test.		Filtrate from Strain.	Filtrate Test.		Neutralisation Test.	
		Test.	Control.		Test.	Control.	Test.	Control.
1	1	++	0	1	++++	0	0	0
	2	+++	0		++++	0	0	0
	3	++	0		+++	0	0	0
2	1	++++	0	2	++++	0	0	0
	2	0	0		++	0	0	0
	3	++	0		++++	0	0	0
	4	0	0		++	0	0	0
3	1	++++	0	3	++++	0	0	0
	2	++	0		++++	0	0	0
	3	0	0		+++	0	0	0
	4	0	0		+++	0	0	0
4	1	0	0	4	+++	0	0	0
	2	0	0		+++	0	0	0
	3	++	0		+++	0	0	0
	4	++++	0		++++	0	0	0
5	1	+++	0	5	++++	0	0	0
	2	0	0		++	0	0	0
	3	+++	0		+++	0	0	0
6	1	0	0	6	++	0	0	0
	2	+++	0		++++	0	0	0
	3	0	0		+++	0	0	0
	4	++++	0		++++	0	0	0
7	1	+++	0	7	+++	0	0	0
	2	+++	0		+++	0	0	0
	3	++	0		++	0	0	0
	4	0	0		0	0	0	0
8	1	++++	0	8	++++	0	0	0
	2	0	0		++	0	0	0
	3	0	0		+	0	0	0
	4	0	0		0	0	0	0
9	1	0	0	9	0	0	0	0
	2	0	0		+	0	0	0
	3	++	0		+++	0	0	0
	4	++	0		+++	0	0	0
10	1	++++	0	10	++++	0	0	0
	2	+++	0		+++	0	0	0
	3	++	0		++	0	0	0
	4	0	0		+	0	0	0
11	1	0	0	11	+++	0	0	0
	2	0	0		++	0	0	0
	3	0	0		++	0	0	0
	4	0	0		++	0	0	0
12	1	++	0	12	++++	0	0	0
	2	0	0		+++	0	0	0
	3	++	0		++++	0	0	0
13	1	0	0	13	0	0	0	0
	2	0	0		++	0	0	0
	3	++	0		+++	0	0	0
	4	0	0		+	0	0	0
14	1	0	0	14	0	0	0	0
	2	0	0		++	0	0	0
	3	++	0		+++	0	0	0
	4	0	0		+	0	0	0

streptococci are really immune to scarlet fever, or that they are protected by a local immunity mechanism. In the case of the Schick test an accurate method of measuring the toxin has been devised and further, it has been definitely ascertained that $\frac{1}{30}$ to $\frac{1}{50}$ of a unit of antitoxin per c.c of human serum is required to give protection against diphtheria. The toxin used at present for the Dick test may therefore require further standardisation in order to make the Dick test results comparable to those obtained with the Schick test. Meantime scarlatinal and non-scarlatinal types of hæmolytic streptococci, if such exist, cannot be distinguished by the methods described above.

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THE DREYER AND WARD SIGMA REACTION IN CONGENITAL SYPHILIS

BY

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In a report to the Medical Research Council [1] of 1,342 cases examined by the Harrison, Fleming and Dreyer methods, Houston, Campbell and Smyth working in the same Unit showed the accuracy and greater sensitiveness of the Sigma technique in the diagnosis of syphilis. These investigators also found that "the flocculation test of Dreyer and Ward was an interesting and valuable method of determining the progress of a case of syphilis under treatment."

Since 1921, 52 cases of congenital syphilis attending the V.D. Department of the Royal Victoria Hospital and referred from the Belfast Hospital for Sick Children have been submitted to this test. All the cases have not been examined by the Dreyer method owing to the difficulty in many instances of obtaining the necessary quantity of blood (7 cc.). Otherwise there has not been any selection of the cases.

It was noted that all cases of clinical congenital syphilis showed a definitely positive Sigma reading, *i.e.*, greater than 1.5, and that the Wassermann reaction by the Harrison and Fleming methods was also positive. It was also seen that no case had a Sigma reading of 0 even after prolonged treatment, extending over five years in some cases. A few readings of a value under 2 were, however, recorded. The general tendency was for the Sigma to assume a lower figure in response to treatment.

Of the 52 cases considered, 24 were suffering from eye affections. This proportion (46.1%) almost coincides with that noted by Jewesbury[2], viz., 42 out of a total of 84. It is possible that this high percentage is due to the desire for treatment for affections which cause more physical discomfort than many of the other manifestations of the disease. Of these 24 cases, 20 showed a Sigma reading over 10, 17 were over 30, and 5 were over 200, when first presented for treatment.

There were four cases of iritis with the Sigma ranging from 59 to 94. One of these was under treatment for 26 months and by then had a reading of 1.8. In another, as a result of the first month's treatment, the Sigma fell from 94 to 33. This feature of a marked preliminary fall was noted in many cases in the series, and was usually followed by a much more gradual decline in the succeeding months. The accompanying illustration represents this

graphically. There was one case of iridocyclitis under observation for almost five years, the Dreyer reaction being done 13 times. In spite of treatment the Sigma did not alter materially, although the clinical condition improved

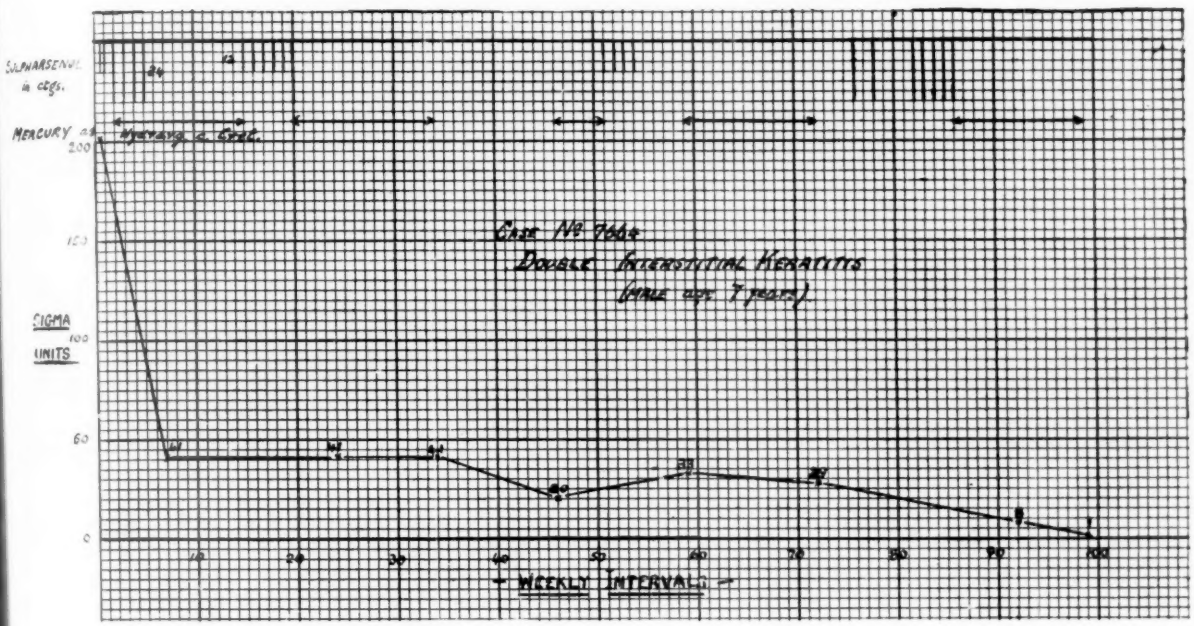

Chart showing the Sigma readings at weekly intervals in a case of Congenital Syphilis undergoing treatment: a rapid fall is followed by a more gradual decline.

decidedly, the eyes being reported "clear" after 23 months' treatment. There was one child with maculæ who had a Sigma of 9 eventually reduced to 3. Clinically she was reported "improved."

There were 13 examples of interstitial keratitis, 9 in girls, the ages ranging from 6 to 17 years, 7 of them being in the age group 6–8 years. The highest Sigma reading was 314, other high readings being 201, 190, and 115. One had a reading of 6 when the first Sigma was obtained, the eyes were reported "clear" in 12 months, and after a further 12 months' treatment the Sigma was 1.8, *i.e.*, a virtual negative. The Harrison and Fleming tests were negative. One of these cases is set out in the form of a graph showing how the Sigma was lowered in the course of 105 weeks' treatment, from 201 to 1, the Harrison and Fleming being negative at the end of that period. In another case the fall was from 190 to 16 after two months' treatment: in another from 115 to 57 after nine months. To demonstrate how difficult it is to obtain a low Sigma, Case 6,343 is of interest. The first Sigma obtained was 45 in June, 1924, after two months it was 15, and in spite of treatment varied between 9 and 15 until February 1926, when it was 7. In September 1926, it was still 7, although the clinical condition was reported as "much improved." Another feature noted was that the lower the original Sigma, the less spectacular the immediate

response. In Case 3,930, in June, 1923, the Sigma was 14.8, the next record was 6.8 and in February, 1926, it was 3.6 and in May, 1926, 2.2 ; the Harrison and Fleming being ++ throughout.

In the series, two cases of condylomata occurred, one in a female of 13 years, and the other in a male infant of two years. In the older patient the Sigma was 79 in June, 1922, and in three months it was 2, with a negative Harrison and positive Fleming. The infant had an original Sigma of 384, and after five months' treatment it was 65.

In an infant of one month, who had " snuffles " and whose father was known to have syphilis, blood was obtained from the superior sinus and the Sigma was found to be 100. After a year's treatment it was 6.9 with Harrison+ and Fleming+.

There were three cases in which the retina or choroid was affected, the Sigma readings being 83, 70, and 8.3. In two of these the figure reached a low level after 16 months' treatment. In the third case where the Sigma was 8.6, after two months it was 16, and it then gradually subsided to 1.6 in seven months with a negative Harrison and Fleming. This preliminary rise after the initial treatment was noted in a number of cases, and may possibly be explained as a modified Herxheimer reaction.

Ulceration of the mouth, palate and tonsil, and nasal necrosis were diagnosed in 13 cases referred to the department for treatment. The ages varied from 9 to 17 years, 7 being in males. The Sigma reading in this group was rather high ; in six cases it was over 100, and in one 930. As a result of treatment much lower figures were obtained, but only after a lengthy period. Clinically the local lesions cleared up rapidly, but in no case did the Sigma register 0. In three cases the Sigma was reduced to a figure less than 4. One case (2,381) was under observation and treatment for over five years. In November, 1921, the Sigma was 118, in six months it was 53. There was no material change for twelve months, 44 being the figure in March, 1923. In June, 1924, it was 22, and two years and three months later it was 32, and in February, 1927, 12.2. In all 18 readings were obtained, the Harrison and Fleming being positive throughout. In Case 6,378 where the Sigma was 930, the result of two years' treatment was its reduction to 120.

There were nine cases of bone and joint affections (" sabre tibia," periostitis, arthritis) at ages varying from 6 to 16 years. The Sigma ranged from 19 to 279 on first observation, but on the whole, the response to treatment was not marked. Clinically there was a decided improvement in the local lesions, especially where there was ulceration and arthritis. In Case 5,349 where the first figure was 279 there was a steady fall to 7 in thirteen months.

Two cases were referred to the department because of stunted growth and anæmia. In one case the spleen was enlarged. These cases also showed a somewhat lower figure eventually, but the striking feature was the rapidity of growth which took place in both.

The remaining three cases were not under constant observation, and in two cases only one Sigma was obtained. One case was a girl of 11 years with interstitial keratitis, deafness and arthritis with a Sigma of 360, and positive Harrison and Fleming. She had a sister who showed the same congenital manifestations. The father was asked to report for examination, and although he denied infection his blood was examined and found to be negative. The mother had died some years previously of "rheumatism." There were two cases of Hutchinsonian teeth with Sigma readings of 5 and 65.

Owing to the lack of space the amount and nature of the treatment is not shown in this paper, the purpose of which is to show that the Sigma reading is of value from a diagnostic point of view, and indicative of the intensity of the specific toxin. Serial observations over prolonged periods have shown that it requires persistent treatment to reduce the figure to a "virtual negative" of under 1.5. In no case was a figure of 0 recorded either before or as a result of treatment. Attention has already been drawn to the preliminary fall which occurred when treatment was first given, and the more gradual decline later. The higher the original figure the more striking was this preliminary fall. A rise in the Sigma was noted in a number of cases during the progress of treatment, and it is suggested that this may be an indication of a modified Herxheimer reaction. Case 7,644 is set out in the form of a graph indicating the details of the treatment given.

All the Sigma tests in this paper were carried out in the Pathology Unit of the Royal Victoria Hospital, Belfast, and we are indebted to its Director, Sir Thomas Houston, for permission to use the figures. Dr. J. C. Rankin, Physician-in-charge of the V.D. Department, has kindly given us access to the clinical records.

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Notes on a Case of CHRONIC POLYARTHRITIS (Still's Disease) treated by Intravenous Protein Therapy

BY

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The prognosis of the type of polyarthritis which is known as Still's Disease is varied. It is certainly true that in some instances the process comes to an end and recovery takes place. Yet in the majority, at least in my own experience, the disease when once established seems to progress in spasms and while often leaving the general health comparatively unaffected, in the end produces such a degeneration of the powers of resistance that the victims succumb readily to some form of acute infection. Even when recovery does take place the results of the repeated attacks of arthritis often leave a considerable disability in the deformed or anchylosed joints.

It is these considerations which impel me to place on record the details of a case of this disease in which a certain form of treatment, protein shock, appeared all but instantaneously and completely to cure the affection.

The child, a girl, was aged four when she first came under my observation in 1922. At that time she had some thickening of the soft structures and of the synovial membrane of the left knee-joint, together with a considerable and painful effusion into the right knee-joint. In addition, there was swelling of both tarso-metatarsal joints with œdema of the dorsum of the feet, and both wrist-joints were painful and swollen. The joints of the fingers were stiff, but were not painful. At this date the shoulders, hips and spine were unaffected. The spleen could be easily palpated, and was certainly larger than normal: and the glands were enlarged on both sides of the neck, in both axillæ, and in both epitrochlear regions. In fact she was a typical picture of Still's disease. From time to time she had bouts of moderate fever, with increase of pain in the affected joints.

Various attempts were made to endeavour to track the source of infection. Her Wassermann reaction was negative. X-rays shewed some rarefaction of the ends of the bones. v. Pirquet's reaction was negative, and with a subcutaneous injection of bovine tuberculin ·005 grm. there was a slight positive reaction. Fluid from the joint was sterile on cultivation. Lastly, there was no obvious source of infection in throat, mouth, ears or urinary or alimentary tract.

With rest in bed her joint condition improved but directly she was allowed to get up the right knee-joint filled and became painful, She then had the joint placed in plaster for four months. After this she was admitted to the hospital for tonsillectomy although her tonsils were not obviously infected. The removal of the tonsils was followed by acute fever to 102°, and hot painful

swelling of both knee-joints. After an interval these symptoms subsided and she was discharged from hospital walking stiffly but free from fever or pain.

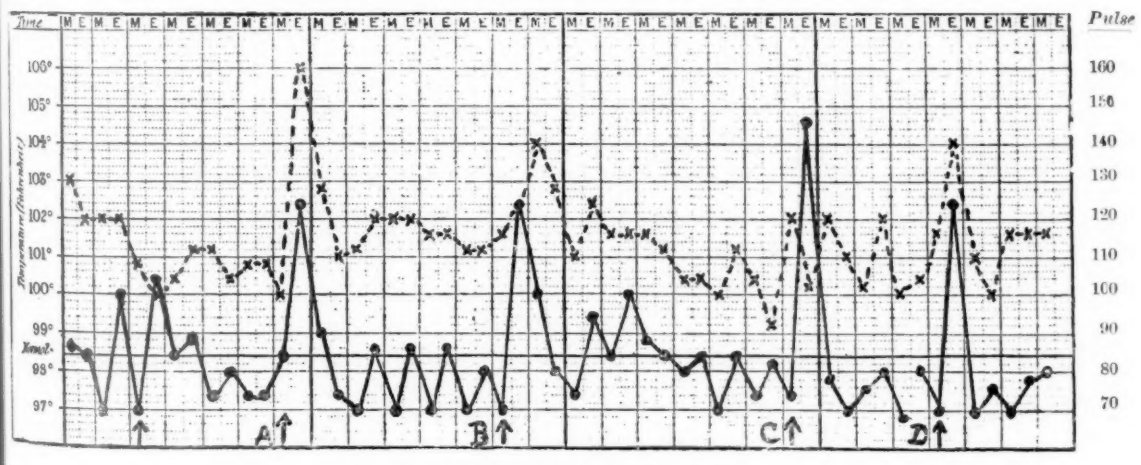
Two months later she had a fresh attack of fever to 103° with painful swelling of both knee-joints, both wrists, and the left elbow-joint. The epitrochlear and axillary glands were again enlarged and the spleen easily palpable.

At this stage I thought that it was permissible to attempt to combat the infection with some form of intravenous therapy, and she was given a ·2 grm. dose of neo-kharsivan: a dose which as the event shewed was poisonous. She had an immediate fever, was very ill with vomiting; on the fifth day from the injection developed a pink urticarial eruption over the whole of the trunk and limbs, and on the fifteenth day was deeply jaundiced with bile in the urine and clay-coloured stools. She had some delirium and wasted very rapidly, and at one time I thought that she was not going to recover. However, the jaundice slowly improved and two months after the jaundice began she was fit to leave the hospital, walking very stiffly with limitation of movement in all the joints which had been affected.

A fortnight later she had fresh joint trouble, more extensive and more severe than at any previous attack. Both knees, both feet, both wrists, and the vertebræ of the neck were involved. She could not be moved at all without much pain. The pain prevented her from sleeping. She had some moderate fever and a marked degree of wasting set in.

At this time she had two or three injections of collosol sulphur, but beyond a slight increase in the range of the fever we could see no benefit.

In July, 1923, she was in such a condition of pain, fever, wasting and general misery that I determined to employ protein shock. I had previously used this method in some arthritic cases in adults, but never before in children. She


Time
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was given intravenously 50 millions of T.A.B. vaccine. This was followed as is usual, in about half an hour, by a severe reaction ; headache, nausea, vomiting, and fever to 101°. At the end of half an hour she went to sleep and woke an hour later, not merely feeling quite well, but with already freer movements of the joints. This rapid relief from pain is often extremely well-marked in adults. In the next four weeks she had four further injections of T.A.B. vaccine, one of 75, and three of 100 millions. Each injection was followed as the chart shows, by severe reaction, rigor, headache, vomiting, and rise in temperature and pulse-rate, but with each injection she showed such marked improvement both in general condition and in the relief of pain and swelling of the joints that we were willing to pursue the treatment. After the fifth injection she had so much improved that she was allowed to get up and shortly afterwards went home.

It is now nearly four years since these events. In that time she has had no return of either pain or swelling, and though there remains some thickening of the synovial membranes of the knee-joints and some thickening of the soft parts round the other joints which were affected, she has no limitation of movement in any joint : she can run and jump, goes to school normally and is making normal progress in weight and height. Her glands are no longer enlarged and her spleen cannot be felt.

There is not, of course, anything novel in the application of this " shock " treatment to a case of arthritis. Gow and others have described some striking examples of refractory joint disease which have been benefited by the procedure. It is known that one of the results of the " shock " is the sudden increase in the number of leucocytes in the peripheral circulation, and Gow believes that this increase is due to the pouring out of new cells from the bone marrow. But it is to me extremely difficult to account by this means for the immediate benefit in the relief of pain, and, in this case, in the rapid, complete and permanent disappearance of a chronic infective disease. Other authors have assumed that the effects of the injections are due at least in part to the flooding of the whole body with ferments and anti-bodies. The proof of such an event is probably not within our present powers, although it has been shewn that in some of the specific infections, such as gonorrhœa, the agglutination titre has been increased.

AN ANALYSIS OF ONE HUNDRED CASES OF FITS IN CHILDREN

BY

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This analysis of one hundred cases of fits in children was undertaken at the Hospital for Sick Children, Great Ormond Street, with the object of discovering the clinical associations of the convulsions, classifying them ætiologically, as far as possible, and determining the effect of treatment.

The children examined varied in age from six weeks to eleven and a half years. By far the most were aged one year or less at the time of onset. Less than half this number began in the second year of life, while in the third year the incidence again rose. After this the incidence of cases gradually diminished; only one case (1%) had fits for the first time in the twelfth year of life.

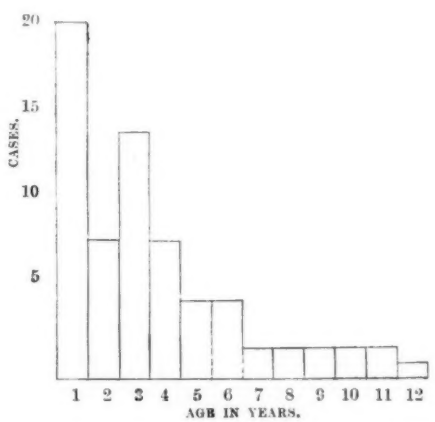

Fig. 1. The Age of Onset of Fits (100 cases).

Fifty-five cases were boys, and forty-five girls; in 20% of cases there was a family history of epilepsy. In one case there was a family, and a personal history of eczema. There was a personal history of cyclic vomiting in one case; in no case was there a family history of cyclic vomiting, asthma, gout, or urticaria. In eighteen instances, there was a history of difficult labour. In twenty-six cases there was a deficiency of mentality, more or less marked; in all the others it was normal. Where mental deficiency was present, it had been noticed as early as the fits; in two cases, mental impairment was stated to be progressive. Of the cases with mental deficiency, eight were born with difficulty; one precipitately, the child's head striking the ground; six had spastic

diplegia ; one was a mongol, one was regarded as post-encephalitic mental deficiency, and two were microcephalic.

The following were the associated clinical conditions noted :—

Spasmophilia	5 cases
Threadworms	2 ,,
Teething	5 ,,
Tuberculous meningitis	1 ,,
Rickets	3 ,,
Diphtheria	1 ,,
After Measles	1 ,,
Broncho-pneumonia	1 ,,
Constipation.....	6 ,,
Head injury.....	1 ,,

The weights of the patients have been plotted on a graph, together with a curve representing average weight from birth to 12 years. It will be seen that the dots are arranged almost symmetrically about the curve, only a slight excess being found below the curve ; this indicates that the average weight of the patients is not much below normal.

Age in years.

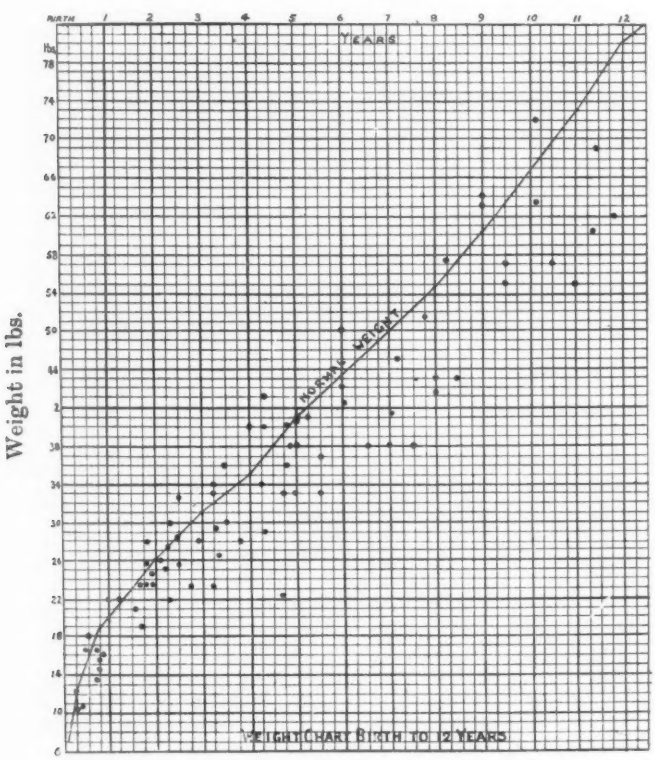

Fig. 2.
Weights of 100 children suffering from Fits, compared with the normal weight curve (0—12 years).

Nature of the Fits.

Cases of petit mal, using the term to include cases in which loss of consciousness was incomplete, were about as numerous as those who suffered from grand mal alone. A relatively small number had both kinds of fit, and in three cases a history was given that whereas the child used to suffer from petit mal this had been replaced in the course of time by major fits. Several varieties of petit mal were met with, but no case was seen of the type termed pyknolepsy, defined by Adie[1] as "a disease with an explosive onset between the ages of 4 and 12 years, of short, very slight monotonous, minor epileptiform seizures, of uniform severity, which persist for weeks, months or years, uninfluenced by anti-epileptic remedies, without impeding normal mental and physical development, and ultimately cease spontaneously, never to recur." There was one child who fitted in with this definition so far as the individual attacks, which were sometimes repeated 40 times daily, were concerned; but the onset was at the age of two, and a year later, he started to have grand mal. There was one interesting case in which the attacks occurred with a frequency varying from a dozen to several score daily. Each consisted of a forward nodding of the head, with a vacant look in the eyes and a twitching of the mouth, lasting about 15 seconds. In the later attacks there was in addition a rhythmic twitching of the arms. The legs were held stiffly if the child was seated when the attack occurred, but no movement occurred in them. In another case the fit consisted in a momentary vacancy with twitching of the hands; in a third there was a glassy look in the eyes, copious salivation, and the left arm was abducted from the side and drawn backwards, and the left corner of the mouth was drawn down. The remainder of the group consisted of cases in which there was merely a transient loss of consciousness unaccompanied by any motor phenomena.

Considering the stage of mental development of the patients, a history of an aura was not often to be expected; it was only elicited in two cases—one a girl of 11, who suffered from grand mal, had a visual aura; the other, also a girl of 11, had a headache before a series of petit mal attacks. In many instances, however, the mother said that she could tell from the child's behaviour when an attack was about to occur. In one case a characteristic change was noted several days before the fit actually occurred. Most of the patients with petit mal, recovered rapidly from their attacks; a few complained of headache, one of loss of memory, and one boy of five had periods of automatism,

The patients with grand mal composed half the total. In four instances fits occurred only at night; in the remainder, they occurred by day and night, or by day only. The cases with established epilepsy were investigated, first, with the object of deciding what exciting factors were concerned in the fits. In four constipation was considered all-important by the parent; in these it was invariably noted that constipation was severe at the time of the fit. Excitement was another factor; in some cases fits were more numerous or occurred only at the week-end; some unwonted excitement at this time was

probably the explanation for this; larger and richer meals may also have played a part. A total and differential white blood count was made in eleven cases. These showed an average white cell count of 8,000, while the various types of white cells were present in proportions which could be regarded as normal considering the ages of the patients. Eosinophil polymorphs averaged 1%. The blood was grouped in nine cases; the results were as follows:—

Case.	Patient's Group.	Mothers' Group.
1	3	–
2	4	2
3	2	2
4	3	4
5	4	4
6	4	4
7	4	4
8	4	2
9	2	–

The distribution of the patients in the different groups corresponds roughly with that of normal individuals, and there is no striking relationship between the blood groups of mother and child.

Lumbar puncture was performed in six cases. No abnormality was discovered in the cerebro-spinal fluid. The protein, chloride, cell, and sugar content were all normal. In all cases the Wassermann reaction was negative. The blood W.R. was also negative throughout the series. The fundus oculi was examined in all cases, and found normal in every one.

Treatment.

The two main methods of treatment used were the usual ones of bromide and luminal. Twenty-five cases of major epilepsy were treated with sodium luminal combined with 10-minim doses of tincture of belladonna. Of these 21 were benefited, two were not improved, and in the remaining two the fits became worse. In many cases the effect of the drug was striking, and in 11 out of the 21 cases that derived benefit, the improvement could be described as very great. The selective action of the drug was demonstrated in one case of combined petit and grand mal. The patient, a girl aged 3, had no major attack for four months after being given luminal, but minor attacks continued with the same frequency as before treatment. The dose of luminal used was variable, and depended, not on the patient's age, but on the individual response. In some cases there was remarkable improvement on $\frac{1}{2}$ grain daily; in others $\frac{3}{4}$ grain was given daily to get the best results; this dose, $1\frac{1}{2}$ grains twice daily, was the maximum. Two cases, treated first with bromide and chloral, with little or no benefit, did well when luminal was substituted. Six cases were treated with potassium bromide; in three the number of fits was uninfluenced; in three they were diminished.

Two cases of spasmophilia were improved with chloral and hydrarg. cum creta, and two other cases which were given cod liver oil and malt and ammonium chloride were rapidly cured. One patient was treated with bromides, and then with luminal, the only result being an increase in the number of fits. As a last resort sub-temporal decompression was done; convulsions started on the evening of the day of operation, and continued till the death of the patient. Post-mortem showed there was no gross lesion except a minute hæmorrhage in the cortex under the site of the decompression. An interesting feature in the history of this case was that the fits stopped temporarily after measles.

TABLE SHOWING EFFECT OF VARIOUS METHODS OF TREATMENT.

	Grand Mal.					Petit Mal.			
Method of Treatment.	Total Treated.	Great Imp.	Mod. Imp.	No Imp.	Worse.	Total Treated.	Great Imp.	Mod. Imp.	No Imp. or worse.
Sod. luminal and Tr. belladonnæ ..	25	11	10	2	2	15	4	2	9
Bromide and Chloral	2	0	0	2	0				
Bromide	6	0	3	3	0	3	1	1	1

The results of treatment in the cases of petit mal were less successful. Fifteen cases were treated with sodium luminal; in only six did it have a favourable effect; four showed marked, two only slight improvement. In nine cases the drug was either without effect, or made the condition worse. The dosage employed, and mode of administration were the same as used for grand mal. Three patients were given potassium bromide; one was greatly improved, another moderately improved, and the third unchanged. One case which resisted all drug treatment was admitted to hospital and treated with the ketogenic diet. No decline in the number of attacks was noticed—they were occurring at the rate of 10—12 daily during the period of treatment—nor did the number increase when the diet was left off. One other case which was resistant to all forms of drug treatment received a special form of treatment. The patient was a girl aged 9 months, who had frequent attacks of petit mal. There was a history of a difficult labour, and difficulty in getting the child to breathe after birth. A decompression in the left parietal region was done, with encouraging results. The number of attacks was considerably reduced.

Discussion.

The first noticeable point is the heavy incidence of the disease in infants less than one year old. Fits occurring at this age are usually associated with trivial ailments such as constipation and teething; in many cases they are

recovered from, and there is no recurrence. But on the other hand many of the cases in this series which had their first fits in early infancy continued to have fits for years afterwards. Of the twenty-three cases in which the onset was in the first year of life, fourteen continued to have fits during the several years they were under observation. The occurrence of convulsions in infancy and their recurrence in childhood after several years of freedom is well known; two examples of this phenomenon were met with. In one case fits occurred at the age of one, and then there was complete freedom for four years, when at the age of five they recurred. In the other there were attacks in infancy; then, again, when the child had pneumonia at three; and then none for two years. From the age five till twelve fits were frequent; at the latter age the child passed from observation. A history of heredity was presented by 20% of cases—a figure which corrseponds closely with that usually given. It was 35% in Gower's cases, and 16% in Spratling's series of 2,523 cases. The sex incidence was found to be roughly equal.

There are many features of epilepsy which suggest an analogy with diseases nowadays thought to be due to an abnormal sensitiveness of the tissues—such as asthma, urticaria, eczema, cyclic vomiting and gout. This investigation revealed, however, practically no association of epilepsy with any of these diseases. A high eosinophil leucocyte count may be found in this type of disease; but in none of the cases under investigation in which blood counts were done, were these cells unusually numerous. Total white cell counts were uniformly within normal limits also. The features of the hæmoclastic crisis of Widal are stated by Bossard immediately to precede an attack. The good fortune to make a blood count immediately before an attack was only realised in one instance, and in this case no leucopenia was present (W. B. C., 7,000). Another feature of Widal's crisis is a fall in blood pressure. There was no opportunity of estimating the blood pressure just before a fit in these cases, but several observers have reported such a fall; it is difficult to know whether this should be regarded as cause or effect. Those investigations which are detailed here are, therefore, not such as will support the view that epilepsy is the result of tissue sensitisation.

Endogenous toxic products have been considered a cause, and this is generally conceded to be the mechanism of the fits of uræmia and eclampsia, of severe liver disorders, and of some pituitary and thyroid diseases. In these conditions the morbid changes are so gross that it is not difficult to believe that there may be a perversion of metabolism with the production of a toxic substance. But in the cases of idiopathic epilepsy so-called, such changes are conspicuous by their absence. Cuneo (quoted by Osnato) believes the primary defect in metabolism occurs in the intestine. He gives the following account of the process: citrates, alkaline tartrates, and other organic salts when painted on the motor cortex produce convulsions; in the normal subject such substances are produced in the gut, but are converted into bicarbonates, a process which begins in the gut and is completed in the liver. In epileptics this transformation fails to occur; the organic acids reach the

brain and there have an action on the nucleo-histones of the cell-nuclei which results in the precipitation of nucleinic acid, and a base which has all the properties of proteose remains in solution. The latter is capable of producing typical convulsions in animals. Cuneo attempted to combat these dangers, by giving alkalis by the mouth, a low starch diet, and the subcutaneous injection of nucleinic acid in alkaline solution. He claimed good results. Some investigators believe vaso-constriction in the region of the motor cortex to be the cause of epilepsy ; and fits have been produced experimentally in this way. Cuneo believes that here also the mechanism he describes is involved, the anæmia resulting from vaso-constriction leading to increased acidity of the tissues, and consequent liberation of a proteose-like substance from nucleo-histone.

Directly opposed to the above view is one which has its origin in America. This supposes that epilepsy results not from an acidosis but from an alkalosis, since acidosis is associated with many of the conditions having a favourable effect on epilepsy ; for example, ether anæsthesia, and acute infections during and after which epilepsy may subside. A form of treatment based on this view has been evolved ; it consists in a diet rich in fat and poor in carbo-hydrate (ketogenic diet). Such a diet tends to alter the reaction of the blood in the direction of acidity, and starvation has the same effect. The exponents of this method report good results—a temporary amelioration of the epileptic symptoms in some cases, a complete disappearance of the attacks in others, that is, up to the time of publication, the periods of observation being not longer than six months. In the one case of the present series treated by this method, no benefit whatever was observed. Some authors of the various explanations which have been suggested for the production of idiopathic epilepsy also apply their views to those cases of fits associated with gross changes within the cranium. Cuneo, for example, supposes that in cerebral tumours, tissue breaks down with the liberation of the convulsant proteose. Again, Sargent explains the fits following cranial trauma, as being the result of reflex vaso-constriction from tension or adhesions. Such vaso-constriction, according to Cuneo, would produce convulsions by the decomposition of nucleo-histone as described above. Possibly the fits occurring in cases of spastic diplegia, and in cases giving a history of difficult labour, are to be explained along these lines.

A distinct line of thought finds its expression in the psychogenic conception of epilepsy. This was propounded by Pierce-Clark who defines epilepsy as a " psycho-biological reaction which is a refuge from an intolerable adjustment demand, and which constitutes a regression to a primitive pleasurable state." On this view the condition arises from a primary psychological defect. The mentality of the patient is characterised by egocentricity, hypersensitiveness, and emotional poverty. Such individuals find the strain of trying to cope with their environment too great, and escape from it by means of a fit. But a purely psychological explanation is obviously inadequate, since the mechanism of a physical process must be, essentially, a physical one. As a matter of fact,

however, mental processes do play a considerable part in the disease under consideration; epilepsy sometimes arises in the adult after a prolonged period of mental strain, and such cases were not uncommon as a result of the war. Also depressing or exciting emotion may be the immediate precursor of the individual attack; as was noted in many of the children investigated. A suggestion of the link between these mental changes and the physical basis of an epileptic attack is provided by some work of Cannon's. Experimenting on cats, this observer showed that prolonged painful stimuli, and conditions of fear or anger, lead to an increase in adrenalin content of the blood. The increased concentration of this hormone in the blood may lead to constriction of the cerebral arterioles, and so produce a convulsion. This sequence of changes, vaso-constriction followed by a fit, is observed when adrenalin is painted on the cortex. The psychogenic conception will probably only be the explanation in a small number of cases, and would seem to have its most limited application in children, in whom the "adjustment demand" is not likely to be so intolerable as to produce convulsions.

Epilepsy has been a common disease since the time of Hippocrates, yet we know little more about it than this observer. The modern trend of opinion is towards some metabolic disturbance as being the cause; our ignorance as to what this distrubance is, is sufficiently indicated by the multiplicity and mutual antagonism of the various views taken of its nature.

A comparison of the results of treatment with various drugs shows that luminal gave easily the best results. In all cases it was combined with tincture of belladonna. The results are very different in the major type of fits, from those obtained in the minor cases. In the latter only a minority are improved, although the results are better than with any other drug. In the treatment of major fits in children, luminal was found, combined with belladonna, to be a distinct advance on bromides. Using two other methods of treatment, the ketogenic diet, and cerebral decompression, no benefit was obtained using the former in one case, while the latter resulted in definite relief in one case, but proved fatal in another.

The observations recorded here were made on patients attending Dr. Donald Paterson, to whom I am indebted for help.

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A Case of CONGENITAL ATRESIA OF THE JEJUNUM (with Recovery)

BY

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Of the various forms of congenital malformation few, if any, have been, up to the present time, so uniformly fatal as congenital atresia of the small intestine. From the nature of this condition with complete blocking or loss of continuity of the alimentary canal, it is obvious that an operation affords the only hope of life, and a study of recorded cases shows that only a very few infants have survived.

Davis and Poynter (1) collected 392 cases on congenital occlusion of the intestine between the pylorus and the rectum. Of these, 194 were examples of a single atresia of the duodenum or jejunum, and 67 were cases of multiple atresia, slightly more than fifty per cent. of the latter consisting of from two to nine occlusions of the jejunum and upper ileum. None of the cases of this series recovered; in one of atresia of the jejunum external enterostomy was performed and the infant died six hours later.

Sheldon (2) collected 28 cases from the record of autopsies performed at the Hospital for Sick Children, Great Ormond Street, London, since the commencement of the present century, but no mention is made of any attempt by surgery to avert the fatal issue.

The first attempt at cure by operation was made by Bland Sutton. The first case in which operation was performed successfully was reported by Fockens (3) who made an anastomosis between the segments. The second successful case was reported by Ernst (4) who brought the ileum up anterior to the colon and anastomosed it to the duodenum. The third case is reported by Richter (5) of Chicago, who performed posterior gastro-enterostomy.

As far as we are able to discover the case here reported is the fourth successful case on record, and we are publishing it in the hope that others will soon follow, for with early diagnosis and surgical intervention, we consider that the prognosis of congenital atresia when single and situated in the upper small intestine is by no means hopeless and that a fair proportion of cases should recover.

The degree of vitality displayed by the new-born is occasionally surprising, and one of us has seen an instance of congenital atresia of the small intestine in which the infant survived for more than three weeks, though no food was retained by the stomach after birth and no attempt was made to prolong life by means of subcutaneous injections or other means.

A female infant, nine days old, was seen by one of us in consultation with Dr. Gladys Montgomery on September 29th, 1926, for persistent vomiting. Nothing abnormal had been noted about the baby for the first three days of life except that very little meconium was passed. On one occasion only a small amount of brownish fluid had been passed. Vomiting commenced as soon as lactation was established; it had persisted ever since and was projectile in character. Occasionally a feed was retained, but this was seldom, and it was noticed that after the next feed a larger amount was ejected. The baby, which had weighed 7 lbs. at birth, now weighed only 5½ lbs.

On examination it was found to be feeble, wasted, with loose folds of skin over abdomen and limbs, subnormal temperature, and sunken fontanelle. A feed was given and promptly and forcibly ejected; the vomited fluid being deeply stained with bile. Gastric peristalsis was visible in short waves which stopped abruptly at the mid-line of the epigastrium.

A diagnosis of congenital atresia of the duodenum was made and it was decided to give the baby the benefit of the very slender chance that operation offered for recovery. It was admitted to the Auckland Hospital on the same evening and on the following morning, after preparation with subcutaneous salines and administrations of saline and glucose by the rectum, laparotomy was performed.

The stomach and duodenum were found to be much dilated, the latter ending in a little bulge behind the peritoneum over the lumbar spine. There was no cord or other vestigial structure connecting this mass with the proximal end of the jejunum. The commencement of the jejunum could not be distinguished, for the end of the uppermost loop apparently disappeared into the extra-peritoneal space. The coils of collapsed small intestine all lay in the right upper quadrant of the abdomen; there appeared to be fewer coils than usual, and they overlaid the ascending colon and cæcum. The large bowel was normal in appearance, but there was no great omentum.

As the child was nearly moribund it was not thought advisable to join the extraperitoneal knob of duodenum to the jejunum lying some distance away, for the quickest operation that could be done was anterior gastrojejunostomy. Immediately this was finished the distension of the stomach and duodenum disappeared by the filling up of the coils of small intestine.

For the next three days the condition of the infant was critical, the vomiting persisted to some extent, and often large quantities of bile-stained fluid were returned. However, by keeping the infant in a sitting position, and washing out the stomach with a 5% solution of Sodium Bicarbonate, improvement took place and some of the feeds were retained.

Breast feeding was resumed on the sixth day after operation, and the baby was sent home to be nursed on October 9th. At that date vomiting of clear, bile-stained fluid occurred two or three times a day; the motion was normal, and the baby had gained in strength, and weighed 5 lbs. 10 ozs.

Twelve days later, as vomiting still continued, and the baby had lost a few ounces in weight, she was readmitted for a second operation.

It was obvious that a great deal of the secretions of the liver and pancreas, which had to pass into the stomach on the way to the intestines, were lost by vomiting, and it was therefore decided to make a short circuit between the duodenum and the jejunum.

This, which proved to be a somewhat difficult operation on such a tiny infant, was accordingly done on October 22nd. The anterior aspect of the second part of the duodenum was joined to the jejunal loop distal to the previous anastomosis.

Vomiting occurred shortly after operation and the baby became extremely dehydrated, and too feeble even to suck.

Blood transfusion into the longitudinal sinus was performed and saline was given subcutaneously. On the third day after operation, when apparently moribund, gastric lavage with sodium bicarbonate solution (5%) was successful in arresting vomiting, and thereafter recovery was uninterrupted.

On the sixth day breast feeding was resumed and the baby was discharged from Hospital on November 11th, when she weighed 4 lbs. 14 ozs., to report as an out-patient. On November 16th she appeared quite well; weight 5 lbs. 10 ozs.

On December 7th her weight was 6 lbs. 12 ozs., and on December 29th she was quite well and weighed 8 lbs. 2 ozs. There had been no vomiting for some weeks except that occasionally a small quantity of yellow fluid was returned. On January 30th, the weight was 9 lbs. 12 ozs. and on February 13th 10 lbs. 12 ozs.

The baby was now in excellent health, bright and intelligent.

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A NOTE ON GLUTEAL WASTING AS A SIGN OF CŒLIAC DISEASE.

BY

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As far as I know attention has not been called to a sign which I have often found to be an aid in the clinical recognition of cœliac disease, namely, wasting of the buttocks.

This is seen at a comparatively early stage of the disorder and is apt to persist for a long time, even where improvement is otherwise occurring satisfactorily under treatment. The degree of gluteal wasting varies to some

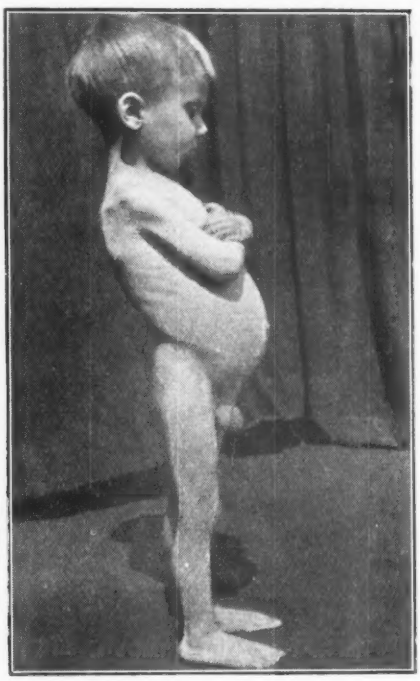

Fig. 1.—R.N., aged 4½. Cœliac infantilism: considerable emaciation; buttocks completely flattened, so that thighs appear set into trunk like the wooden limbs of a toy.

extent according to the general nutrition of the patient. In a plump child the buttocks look merely small; in a very wasted child they look flattened and atrophied. Yet, in my opinion at least, the degree of wasting in the gluteal region is disproportionately greater than that in the rest of the body, and it is this that gives the sign its diagnostic value.

The accompanying illustrations show the appearance of the buttocks in three cases of cœliac infantilism in different conditions of nutrition.

Case 1. R.N., male, aged 4½, a very emaciated, stunted example of untreated cœliac infantilism. The buttocks are much atrophied and flattened almost out of recognition, so that the stick-like thighs appear to be set into the trunk like the wooden limbs of a toy (Fig. 1).

CASE 2. S.T., male, aged 6, a slight and small child with partially treated cœliac disease. The wasting of the buttocks shows well here, for the child is fairly well covered and the lower limbs are thin but shapely, yet the gluteal region is both very small and flat (Fig. 2).

CASE 3. F.S., female, aged 7, a plump but very stunted untreated case. The buttocks are seen to be rounded but very small. The patient is standing next to a normal child a year younger than herself to demonstrate the degree of stunting of her growth (Fig. 3).

I have not met with quite the same disproportionate wasting of the buttocks in other conditions which may, pending an examination of the fæces, be mistaken for, or confused with, cœliac disease. Thus in cases of chronic diarrhœa (as, for instance, from infection by *Lamblia Intestinalis*), or of persistent intestinal indigestion and toxæmia, the history of illness, the symptoms and general appearance of the child may often give rise to a suspicion

Fig. 2.—S.T., aged 6. Cœliac infantilism: general nutrition fair; buttocks small and flat.

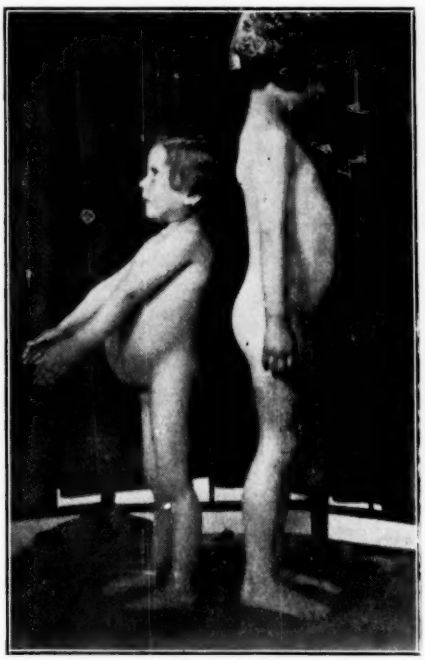

Fig. 3.—F.S., aged 7. Cœliac infantilism: plump but much stunted in growth; buttocks rounded but very small. (The taller of the two children is a normal child of six for comparison.)

of cœliac disease, especially if the milder, non-diarrhœic types as well as the classical type of the disorder are kept in mind. A glance at the back view of the patient may be a guide in such circumstances: where wasting of the buttocks is conspicuously present, it is a point much in favour of a positive diagnosis of cœliac disease.

This small diagnostic point, the gluteal wasting, may well be associated in one's mind with the other symptoms which occur in the lower extremities in cœliac disease; namely, pains, difficulty in walking, and loss of knee-jerk. Of these the last named is the most constant.

CONTRIBUTION TO THE STUDY OF THE AUTONOMIC NERVOUS SYSTEM IN CHILDREN

BY

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The observations of E. F. Müller (1) on the decrease in number of the white blood-cells in the peripheral blood consequent upon certain forms of skin irritation have given rise to a heated debate. Some authors are of opinion that this reaction is due to a biological action of the skin; others compare Müller's results with Widal's "hæmoclastic crisis"; others, again, think the change in the number of leucocytes is produced differently in healthy and in sick persons, obeying no rule.

There are many different ways in which the change in the number of leucocytes can be brought about. E. F. Müller gave intradermal injections of inert and of physiological solutions, and even of distilled water. Others injected hypertonic and hypotonic solutions, and solutions of the salts of potassium, calcium, magnesium, etc., and observed the change in the number of leucocytes following such injections. Other ways of obtaining the reaction are:—injection of cooled solutions, painful in themselves; cauterization of the skin by the application of concentrated acids or alkalies; causing pain by pricking the finger-tips, etc. It is also possible to produce the same reaction by freezing the skin with ethyl chloride, as in the production of local anæsthesia. These irritants, for the most part act on the sensory nerve endings, and by the same means cause different reactions.

The first to make these discoveries was E. F. Müller. He noted that a more or less rapid decrease in the number of leucocytes followed intradermal injections even of inert solutions, the decrease in the peripheral blood being very marked in certain cases. By further experiments he found that, simultaneously with the peripheral leucopenia, a dilatation of vessels and a leucocytosis occurred in the liver and mesentery; whereas a peripheral leucocytosis was accompanied by vaso-constriction and leucopenia in the liver and mesentery. If such be the case, as vaso-dilatation results from parasympathetic influence, and vaso-constriction from sympathetic influence, I think that the impulse must run through a reflex arc, beginning in the skin and ending in the terminations of the vegetative nerves. In the whole reaction the following are called into play:—

1. The skin, with the nerve-endings in it.
2. The centripetal arm of the reflex arc (the sensory nerve or vegetative nerves of skin and vessels).
3. The connection between centripetal and centrifugal arm.
4. The centrifugal arm (the autonomic nervous system of the "cavum abdominis" or of the vegetative organs in general).
5. The terminations of the vegetative nerves in the blood-vessel and in the vegetative organs in general.

6. The physico-chemical medium.
7. The white blood-cells, and their number, under certain conditions. Also, certain vegetative centres.

A somewhat similar reflex is concerned in the secretion of gastric juice and of saliva in response to ocular, olfactory or acoustic stimulation.

After due consideration of these statements, I examined a number of children according to these principles. The method was as follows :—The children were examined in the morning before breakfast, or in the afternoon some hours after dinner. Before and during the examination the child was kept in bed and care was taken not to excite nor disturb it in any way. Blood was taken in the usual way from the finger-tip. After the number of leucocytes had been determined, the skin of the upper arm or thigh was sprayed with ethyl chloride until it was frozen over an area of 2 to 3 cm., and the number of leucocytes was determined in the blood taken every ten minutes from the moment of freezing. The blood was taken six or seven times from the same incision, and with the same instrument. This method was chosen because the child was least disturbed by it, and it usually had no psychical effect ; further, the degree of irritation can be accurately adjusted, and is automatically adapted to the temperature of the body and the surroundings.

For my first experiments, I chose cases of measles and typhoid fever ; consequently, leucopenia was present. Ten cases of measles were examined 22 times, and 17 cases of typhoid 28 times.

In the developing stages of measles, and while the rash was first appearing, a decrease of 18-50% in the number of leucocytes was noticeable as a rule ; an average of 29·5%. From the moment the rash began to fade, an increase in the number of leucocytes was usually apparent on irritation of the skin ; here, again, from 18 to 48%, an average of 32·5%.

M. S., 3½ years. *Measles.* (Koplik, conjunctivitis, rhinitis.) Few spots only, behind he ears and on the chest.

Before freezing	..	..	..	6450
After freezing 10 minutes		..	..	3600
20	„	..	..	4850
30	„	..	..	4800
40	„	..	..	3200
50	„	..	..	6050
60	„	..	..	6200

shewing a fall of 50%. (Chart 1.)

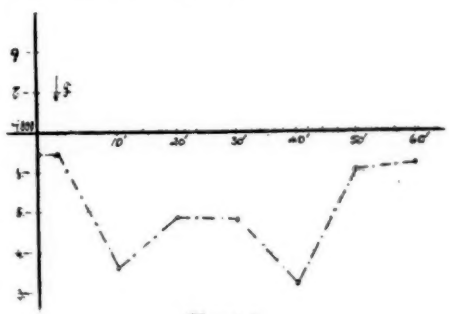

Chart 1.

Same patient three days later; the whole body covered with a thick rash, confluent in some places, in the fading stage.

Before freezing	6400
After freezing 10 minutes	9250
20 „	7100
30 „	7050
40 „	8950
50 „	6400
60 „	7300

shewing a rise of 44%. (Chart 2.)

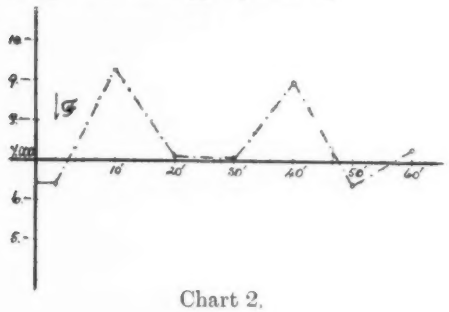

Chart 2.

Since in all the other cases the same course was observed, I refrain from giving further examples.

In cases of typhoid fever, an average decrease in the number of leucocytes of 32% was, as a rule, noticeable during the whole course of the disease.

A. B., 11 years. *Typhoid Fever.*

Before freezing	3700
After freezing 10 minutes	3450
20 „	2700
30 „	2700
40 „	2500
50 „	3150
60 „	2550

shewing a fall of 32%. (Chart 3.)

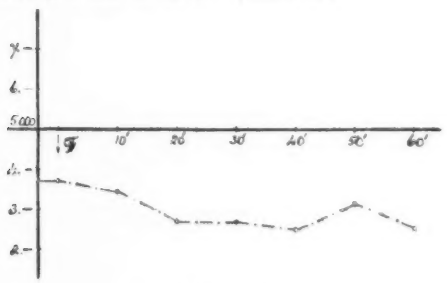

Chart 3.

During these experiments I proved that the tests could only be carried out, in cases of typhoid, when the temperature of the patients was not high. Possibly irritation of the sympathetic centres was caused by the pyrexia or by acidosis.

I followed up these two leucopenic diseases and proved that such simple irritation produced a fluctuation in the number of leucocytes which varied with the disease, and with the stage of the disease, but not with the individual.

It is not possible to ascribe this fluctuation, on such slight irritation, to an increased formation or destruction of the white blood-corpuscles; for it there must be some other explanation. As already mentioned, E. F. Müller found, simultaneously with peripheral leucopenia, a dilatation of the vessels of the liver and splanchnic region and an accumulation of leucocytes in this region: with peripheral leucocytosis, he found vaso-constriction and leucopenia in the splanchnic area. It is a well-known fact that with enlargement of the lumen the rate of flow diminishes, and that friction varies inversely as the rate of flow. Further, elements of lower specific gravity accumulate in the peripheral zone of the blood-stream and those of higher specific gravity in the centre. As the leucocytes are lighter, they accumulate in the peripheral zone, and there they increase when the vessel dilates, on account of their viscosity and the increased friction. In consequence of this, the flow of leucocytes to the heart is diminished, and thus fewer come into the general circulation. The contrary happens in consequence of contraction of the vessels in a more extensive region. This mechanical process may not be enough to account for the increase or decrease in the number of leucocytes in certain regions. This regulation can hardly be caused by purely physical means. The idea is very attractive that it might be brought about by the influence of the vegetative nerves. For, where a constriction of the vessels occurs, occasioned by the influence of the sympathetic nerves, the number of leucocytes decreases at the same time, as if the impulses emanating from the irritated sympathetic metabolites drove away the leucocytes. On the other hand, where vaso-dilatation takes place under the influence of the parasympathetic, an increase in the number of leucocytes is noticeable; thus, the irritated state of the parasympathetic system reacts on the leucocytes, causing them to accumulate in the irritated area. The reaction varies in intensity with the capacity of the blood-vessels in the region affected.

Constriction and dilatation of blood-vessels is controlled by the sympathetic and parasympathetic nerves. If this be so, the whole of the above-mentioned reaction works through these two systems. Thus we find also leucopenia in the blood-vessels of the ear and leucocytosis in those of the mesentery on irritation of the vagus (in dogs) by electrical methods, and the reverse reaction on irritation of the splanchnic nerves (W. Filiuski[2]). Similar results are observed following the injection of sympathetic or parasympathetic poisons. But one must be careful in criticizing the results of injection of these poisons. Every irritant has an effect not merely on one system but on both; so have the poisons. Since the effect is on both, the degree of irritation may not be equal, nor does it necessarily take effect at the same time; the result varying with the dose and the susceptibility of the individual. The more complicated the mechanism by which the results are brought about, the more difficult it is to account for them and to draw correct deductions. The phenomena

described are not merely a demonstration of the parasympathetic and sympathetic systems, but depend upon a conglomeration of different influences which can only be isolated with difficulty owing to lack of control over the stimulus. All this must be borne in mind in the pharmaco-dynamic examination of these systems. I always employed the freezing process, because I thought the reaction caused thereby is not dependent on the impulse nor on the irritant itself, but merely on the state of both systems and on their relation to each other.

Twelve children with an artificial alkalosis caused by $NaHCO_3$, and seven with an artificial acidosis from NH_4Cl, were examined by the above method. If the results obtained from this method may be regarded as a criterion of the state of the vegetative nervous system, then in alkalosis there must be a decrease in the number of white corpuscles in the peripheral blood, and in acidosis an increase, for it is an established fact that parasympathetic influence is associated with an increase of blood-alkalinity and sympathetic influence with a decrease of it (K. Dresel[3]). My expectations were not disappointed. The experiment was carried out in the following manner :—The reaction of the vegetative nervous system was ascertained in the morning before breakfast, and afterwards the patient was given three doses of $NaHCO_3$, each dose amounting to 1–1·5 g. per 10 Kg. of weight, and the following morning an hour before the experiment a further dose of 1–1·5 g. per 10 Kg. of weight was administered. The test was also made with NH_4Cl. The experiment showed that acidosis or alkalosis caused in this manner can often diminish and even change the parasympathetic reaction into sympathetic, and *vice versa*. The reactions can also be intensified. It must be mentioned that the administration of NH_4Cl may cause unpleasant symptoms such as nausea and vomiting, which may vitiate the whole experiment; it is, therefore, advisable to select for examination cases which are not subject to such symptoms. If it should happen that the reaction does not fulfil one's expectations, it is necessary to assure oneself that the condition of the organ under observation is such as to permit of alteration in the reaction. With regard to the importance of this point it is enough to mention the experiments on the hypogastric nerve of pregnant and non-pregnant cats; the gravid uterus responds to stimulation of this nerve with contraction, the non-gravid with relaxation (E. Schilf[4]).

As all experiments had the same result, I mention only the two following cases :—

H. B., 5½ years. *Faucial diphtheria.*

Before freezing	5650
After freezing 10 minutes	7050
20 ,, ...	7250
30 ,, ...	6600
40 ,, ...	7350
50 ,, ...	8050
60 ,, ...	6300

shewing an increase of 42·47%. (Chart 4.)

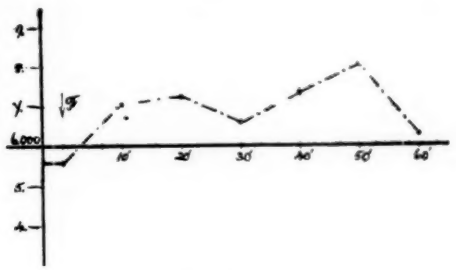

Chart 4.

The same day 7 g. of $NaHCO_3$ was given in three doses. The following day a dose of 3 g. was administered, an hour before the experiment was made.

Before freezing	6750
After freezing 10 minutes	5600
20 ,, ...	6700
30 ,, ...	5800
40 ,, ...	5250
50 ,, ...	5450
60 ,, ...	5800

A decrease of 23·71% is shown. (Chart 5.)

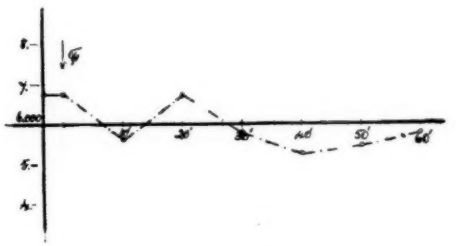

Chart 5.

H. B., 6 years. *Artificial acidosis.* Convalescent from diphtheria.

Before freezing	9650
After freezing 10 minutes	8850
20 ,, ...	9500
30 ,, ...	8750
40 ,, ...	7700
50 ,, ...	7950
60 ,, ...	8950

shewing a fall of 20·2%. (Chart 6.)

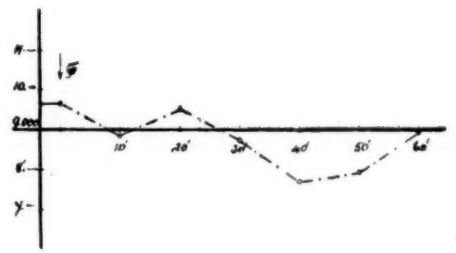

Chart 6.

The same day 4·5 g. of NH_4Cl was given in three doses. The following day, a dose of 3 g. was administered an hour before the experiment.

Before freezing	16000
After freezing 10 minutes	15650
20 ,, ...	21650
30 ,, ...	18750
40 ,, ...	15500
50 ,, ...	14500
60 ,, ...	15150

shewing rise of 29·06%. (Chart 7.)

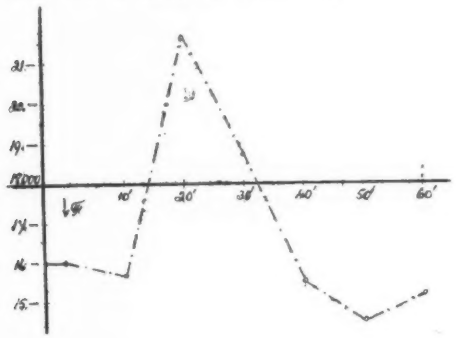

Chart 7.

Conclusion.

From the foregoing results and examination of the literature it is clear that the reaction and the fluctuation in the number of leucocytes following irritation of the skin by freezing are a manifestation of the state of the vegetative nervous system, and finally of the preponderance of one or the other of its parts, taking into consideration the state of the blood and viscera. Therefore I propose this procedure as a method for examining a certain part of the vegetative nervous system.

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THE BONE CHANGES OCCURRING IN RENAL AND COELIAC INFANTILISM AND THEIR RELATIONSHIP TO RICKETS

PART II. COELIAC RICKETS.*

BY

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The occurrence of bone deformities in coeliac disease appears completely to have escaped recognition until within recent years ; a somewhat remarkable fact considering the frequency and the occasional great severity of these changes. Probably some of the cases have not been recognised as due to coeliac disease, and have thereby helped to swell that inchoate group of bone disorders called "late rickets." Another possible explanation of the discrepancy may be found in the fact that many of the earlier descriptions of coeliac disease were instances of the disease occurring in young children, whereas bone deformities do not usually develop before the age of seven years. The stunting of growth and resulting infantilism have, however, been commented upon by many writers, and indeed Gee, in his original description of the disease drew attention to this symptom.

Coeliac infantilism may be defined as the arrest of development and stunting of growth which occurs in that form of severe chronic intestinal indigestion described by Gee and which is characterised by a high grade of defective fat absorption and carbohydrate intolerance.

In the year 1913 when showing a case of coeliac disease before the Midland Medical Society(1) I expressed the opinion that rickets was not an uncommon complication of cœliac disease. As far as I can discover this is the first reference to the occurrence of bone deformities in that disease, although in the previous year McCrudden and Fales(2) had described a case of coeliac disease in a boy aged ten years whose bones showed osteoporosis, fragility and fractures. A contrary view was, however, expressed by Still(3) who, in his Lumleian Lectures, said : "It is indeed a remarkable fact that rickets is rarely found in spite of the long enduring disturbance of nutrition produced by coeliac disease" ; although he did refer to the complication of "late rickets" developing in one case at the age of eight, a girl whose legs at this age began to bend rapidly "so that much distortion occurred, crippling the child." Miller(4) in 1920, in describing a case which showed definite rachitic changes, wrote : "So far as I know such a condition has not previously been described in connection with coeliac infantilism. It is curious that in this disease in which the absorption of fat is so conspicuously defective changes in the long bones are so much less frequent than in renal infantilism. Perhaps the minor manifestations of rickets are missed." Marriott(5) agrees that rickets is not a frequent complication of coeliac disease—"a slight degree of rickets is often observed but no more than in the case of any other malnourished infant or child. Severe rickets is rarely observed in patients with coeliac disease." On the other hand, J. H. Hess, whose original paper I have not been able to consult, is quoted by Abt(6) as saying that rickets was demonstrable in most of his cases. Lichtenstein(7) also

* Part I, "Renal Rickets," was published in ARCH. DIS. CHILD., Vol. II, No. 7, p. 1.

denies that there is any connection between rickets and coeliac disease, but nevertheless found that out of a total of nine cases two showed slight, and three severe rickets. In 1925 Lehman[8] wrote a paper on the bone changes in coeliac disease which was based on a study of three patients all of whom showed osteoporosis and also developed rickets at a very late period of the disease. The most recent contribution to this subject is by Lehndorff and Mauntner[9] who in the course of a comprehensive paper on coeliac disease express the opinion that rachitic bone changes do not occur at all frequently, although they admit that severe forms of rickets may occur at the height of the disease.

In my opinion bone changes are of frequent occurrence in severe cases of coeliac disease, provided that the disease be one of long standing. In not a few cases deformity of moderate degree occurs; rarely there are very severe deformities with multiple fractures. I hope to show in the course of this paper that these changes are rachitic in origin, that they are curable, and that their onset can be prevented.

Clinical Characteristics.

The children, of course, present the characteristic appearances associated with coeliac disease, i.e., pallor, loss of weight, enlarged and atonic abdomen, limbs that are flabby, wasted, slender and hypotonic; and marked arrest of development. The most common bone deformity is genu valgum which varies in degree but which may eventually become so severe that the child "goes off its legs" entirely. Associated with the genu valgum, but sometimes occurring independently of it, there may be some enlargement of the epiphyses of the wrists. Whilst these are the commonest manifestations, the deformities may reach a degree which eclipses the severest grade of rickets which I have seen.

A boy (B. D.), aged 10½ years, when admitted to hospital on August 10th, 1925, measured 38½ inches in length and was unable to walk or to lift himself into a sitting from a prone position, although if sat up he could retain his position. The ribs showed a very marked rosary, the costo-chrondral junctions being enormously enlarged. There was a deep Harrison's sulcus and extreme eversion of the ribs. The whole thorax was small, appeared shrunken, and contrasted greatly with the large and distended abdomen. The clavicles were bent almost to a right angle at the junction of their inner and middle thirds. A degree of kyphosis was present. The humeri showed extreme bending to a point just below the surgical neck, and there was marked enlargement of the epiphyses at the lower end of the radius and ulna on both sides. On the left side there had obviously been a fracture of the lower ends of the radius and ulna with displacement of the bones. The tibiæ and fibulæ appeared fairly straight, but the epiphyses showed some enlargement, and the femora showed severe antero-posterior curvatures.

Bone deformities do not occur unless the disease is severe in type and of long standing, and unless the child has passed the age of seven years. Associated with these bone changes there may be attacks of tetany, a combination more frequently observed in coeliac than in renal rickets. Lehndorff and Mauntner [9] drew attention to the fact that in two of their cases the children showed markedly blue sclerotics. One of my cases also showed this peculiarity but the sclerotics gradually became more normal in colour, and now, some two and a half years after the colour was first noted, they appear normal. The blueness was, however, never of the characteristic homogeneous leaden blue colour that is seen in association with fragilitas ossium.

Radiographic Appearances.

The radiographic appearances of the bones in coeliac disease vary considerably but from a study of them it is, I think, possible to arrive at the method by which the rachitic deformities develop, and also it is possible to watch the process of cure. Still[3] states that skiagrams of the limbs in three cases showed that the " bones were unduly small, corresponding to the small stature of the child, but none showed any abnormality in the formed bone, the trabecular structure was well marked and the outer layer appeared to be normal in thickness and density. They all showed, however, a marked departure from the normal for the age, in respect of the centres of ossification in the epiphyses . . . There is . . . a notable absence of the usual appearance of rickets." The ages of these children are not given, and for reasons which I shall give later this is an important point. If the child be under seven years of age there probably will not be any evidence of rickets, but the bones look unduly small even allowing for the small stature of the child. The trabeculæ may be well formed but should the disease have been present for any length of time the trabeculæ appear to be thinner and the whole bone more osteoporotic and fragile than normal. The cortex also is thinner than would be expected but the epiphyseal line is quite sharp and distinct.

In the case of a child (M. C.), aged 4 years, who had suffered from coeliac disease for three years, my colleague, Dr. Teall, reported as follows: " The radiogram shows very little calcium in the bones which have an atrophic appearance, there is no rickets " (Fig. 1); and again on January 3rd, 1927, that there was marked bone atrophy and that the bones appeared decalcified.

Lehndorff and Mauntner say that this osteoporosis is a very typical occurrence in the course of coeliac disease and that if radiograms were systematically taken in all cases such bony changes would almost constantly be observed, an opinion with which I am in complete agreement.

The earliest evidence of rickets occurs in a bone not very dissimilar from the foregoing, the lower ends of the radius and ulna are slightly enlarged, the spongy tissue a little more open, and there is a slight irregularity at the epiphyseal line. In this form fractures may be present as in the radiogram reproduced (Fig. 2). This was taken from a girl aged ten years, the duration of whose symptoms of coeliac disease was unknown but who had suffered from repeated attacks of tetany since the age of seven.

In a case of moderate severity the radiographic appearances are very striking (Fig. 3). In addition to the delay in the centres of ossification noted by Still the whole bone is atrophic, fragile and osteoporotic. The cortex is thin and the trabecular mesh-work more open and delicate than usual. At the end of the diaphysis there is a well marked metaphysis. The metaphysis is perhaps not quite so splayed out as in ordinary rickets but otherwise there is no difference between the two conditions. Not infrequently in the neighbourhood of the metaphysis are transverse striations: the causation of these has been the subject of some recent investigations to which reference will be made later. Single or multiple, complete or incomplete, fractures of the shaft of the bone are frequently observed. A study of the radiograms (Figs. 3 and 13)

will show the type of changes found better than any written description, and also demonstrates the essential similarity between this condition and what I have called the " atrophic type " of renal rickets.

The radiograms of B. D. show the severest type of coeliac rickets (Figs. 4 and 15-22). When this child was admitted to hospital his bones were so lacking in calcium that it was difficult to obtain a satisfactory radiogram. The osteoporosis was of extreme degree, the cortex of the bone excessively thin and the spongy tissue thin and spidery; indeed, in many areas it was practically non-existent. There were numerous fractures of the ulna and radius, and it was seen that the marked bending of the humeri and the left radius to which reference has already been made were due to fractures. In this instance the usual appearance of a rachitic metaphysis, *i.e.*, the swollen extremity of the diaphysis with an irregular fluffy margin, was not seen. The metaphysis did not appear to be swollen and the end of the diaphysis appeared relatively straight, but at a very much greater distance than usual from the epiphysis. The end of the diaphysis did not, however, present that clear cut sharp outline which occurs in coeliac infants under seven years of age in whom there is not any evidence of rickets; but the picture was essentially what has been described by Wimberger[10] as the " passive type " of rickets. During the process of cure in this case the radiograms approached more closely the appearance characteristic of examples of moderate severity, and the metaphysis lost the appearance of the " passive type " and became more like the usual type of rachitic metaphysis.

The criticism may be made that these radiographic appearances are not those of true rickets, but I would reply that if the radiogram (Fig. 4) be compared with a radiogram (Fig. 5) which was taken from an undoubted case of severe uncomplicated rickets, the picture is seen to be essentially the same.

The series of radiograms (Figs. 1-4) show in my opinion the various stages in the development of the severest type of coeliac rickets. The process and completeness of the cure is also shown in the radiograms reproduced (Figs. 6-12 and 15-22). During the process of the cure the development of transverse striations in the neighbourhood of the metaphysis may be observed (see Figs. 13 and 14). Even after cure is complete the bone is still fragile and osteoporotic, the trabecular network more delicate and the cortex thinner than in the normal bone; but there is no sign of rickets. In this connection it is interesting to note the statement of Park[11] to the effect that although cod liver oil will cure low-calcium rickets, yet it never restores the finer structure of the bone to normal.

The Effect of Growth on the Production of Rickets. Assuming that the deformities are rachitic in nature and that they are due to defective fat absorption, it may well be asked why these changes do not occur in all cases of coeliac disease. I have already stated that these changes are only of frequent occurrence in severe and prolonged cases: these children have in many instances not received efficient treatment. Although such treatment means that the child must be given a so-called fat-free dietary, which is in reality a diet low in fat, yet it does assure the absorption of a certain amount of fat. Thus in one instance when the patient was taking skimmed protein milk only, the fat intake per 24 hours was 7·74 g., of which 94·7 per cent. was absorbed (see O.A., Table 1); whereas if efficient dietetic treatment has not been instituted less fat is absorbed because the disease is more likely to be severe and diarrhœa to occur. It is also possible that in the absence of limitation of carbohydrates a fermentative diarrhœa with consequent non-

absorption of fat will develop. Dietetic treatment does not, however, always prevent the development of rickets, a fact to which attention is drawn under the heading of treatment.

One of the most striking characteristics of coeliac rickets is its non-development before the age of seven years, and its occurrence even at that age only after the disease has been present in a severe form for a considerable time. The explanation of this phenomenon is almost certainly that as long as the child does not grow to any extent rickets will not occur, but that when a period of more active growth arrives, even if that activity be greatly depressed by reason of coeliac disease, rickets will develop. In Part I of this paper the work of Holt, La Mer, and Chown on calcification was quoted, and it was stated that these workers defined rickets " not as a state in which the concentrations of calcium and phosphate are so low that $Ca_3(PO_4)_2$ cannot be precipitated, but as a state in which as the result of lowered ion concentration $Ca_3(PO_4)_2$ is deposited so slowly that the new bone production exceeds in its rapidity, and consequently uncalcified bone or osteoid tissue is produced." In this view, therefore, if growth does not occur, rickets is not likely to develop, even though the ionic concentration be far below that at which rickets usually occurs.

The effect of growth in the production of rickets is probably a factor of very considerable importance. It is well known that children who suffer from infantile atrophy do not develop rickets during that period. McCollum and his associates found that starvation produced healing of rickets in rats, and thought that this effect was due to the liberation into the blood stream of phosphorus derived from disintegrated protoplasm, *e.g.*, muscle, which caused calcium deposition to occur. They came to the conclusions that the starving body is capable of readjusting abnormal relations within itself, and that therein lay the reason why the athreptic child does not develop rickets. I do not think that this can be the correct explanation of the rarity of rickets in atrophic infants when compared with its incidence in other infants of the same age and fed on similar dietaries. I believe that the real solution of the problem of the non-development of rickets in atrophic children is to be found in their lack of growth : " the athreptic child is too busy trying to hold on to life to grow, and not growing—develops no rickets."[13] The parallelism between infantile atrophy and coeliac disease is not, however, quite a complete one, because in the former, with very rare exceptions, the absorption of calcium, phosphorus and fat is normal. Now although defective fat absorption is the cause of coeliac rickets, yet its occurrence also spells starvation and therefore leads to arrest of growth. These two factors (defective fat absorption and starvation) may neutralise one another and prevent the development of rickets until growth occurs ; or to put the same proposition in other words, absorption of calcium and phosphorus, although greatly diminished, appears to be sufficient to calcify the fragile bones of coeliac disease so long as there is little or no growth, but directly any considerable growth occurs this defective absorption results in the development of rickets. Once rickets has manifested itself healing does not appear to occur until the coeliac disease be cured, or unless adequate treatment be carried out, even if growth should again come to a stand-still.

Transverse Striations in the Neighbourhood of the Metaphysis.—The frequent occurrence of these striations in coeliac rickets has already been commented upon. The significance of them has been studied by Harris[13] who holds the view that they constitute evidence of arrest of growth. His observations both on their own merit and because they have received the *imprimatur* of Elliot Smith[14] require careful consideration. According to Harris these lines occur normally in adolescence and in all cases of marked decrease in the rate of growth from any form of acute illness or starvation; they may also occur with seasonal variations in the rate of growth, or as a part of the healing process of rickets. In his view the well-known "line test" of healing rickets is a manifestation of arrest of growth and not, if I understand him aright, a manifestation of healing of rickets. This surely is incorrect, for it is found experimentally that when foods containing Vitamin D are added to the dietary of a rachitic animal, coincidentally with the appearance of the white line growth begins to occur, so that the white line must indicate activity and not arrest of growth. Harris may have more conclusive evidence to prove his theory than he gives in his paper, for the illustrative case quoted is far from convincing. The case was that of a child aged two years and eight months who in three successive years had three distinct illnesses, and who on X-ray examination showed two transverse lines at the lower end of the diaphysis of the femur and the upper and lower ends of the diaphysis of the tibia. The lines were also seen at the shoulder and wrist. These two lines are regarded, but without any proof whatsoever, as being formed during the first and second periods of acute illness. The child later developed a severe attack of broncho-pneumonia, and seven weeks after its onset a radiogram showed a third series of lines of dense bone formed near the metaphysis almost at the ends of the diaphyses. This observation appears to be the only one which can really be cited as evidence in favour of his view, and it does not appear to be sufficient upon which to base his theory. He also makes the statement that the occurrence of these transverse lines has never been reported in cases of genu valgum and it is, therefore, of interest to note their development during the course of recovery in one of my cases (M.R.), a girl who developed such an extreme degree of genu valgum that walking became impossible. These striations are most marked in the radiogram (Fig. 14) taken at the time when the cure of her rickets was completed, and which was, incidentally, the end of the most active period of growth since the onset of coeliac disease. In this instance transverse striations did not develop in the ulna nor in the radius.

The occurrence of transverse striations in coeliac disease is also referred to by Lehmann[8] who in the course of his description of his case says—"in the distal epiphyses of the radius and ulna there are also to be seen a striatification consisting of multiple horizontal lines, so-called 'year rings.' These year rings seem suspicious of past rickets. They are no proof of it, however, since they occur in other nutritional disturbances of the bone." According to A. F. Hess [15] the explanation of the development of these transverse lines "which have been noted and described so frequently in the epiphyses of infants" has always been lacking, but as a rule they have been attributed to

remission in the course of the rachitic process. Now Hess has shown that by giving small amounts of phosphorus to rats, a transverse layer of dense compact osseous tissue immediately adjacent to the proliferating cartilage is produced. The phosphorus, however, is unable to prevent the occurrence of rickets or to exercise any curative effects if rickets be already present. In other words, while phosphorus is able to stimulate calcification at the epiphyses, it is unable to calcify the preparatory cartilage or osteoid tissue. As a result of these observations this writer questions whether some of the transverse striations may not be occasioned by irritative substances similar in action to elementary phosphorus. He has observed these lines develop in infants whose diet and general hygienic surroundings were unchanged, and this has occurred not only during spring and summer but also in the winter months.

I cannot myself offer any evidence as to the cause of the striations, although I have observed them in coeliac disease and other conditions for many years, and I have also pointed out their occurrence in renal infantilism. I have regarded them as representing a period in which better bone was laid down as a result of improvement in the general condition, rather than as an indication of arrest of growth. The case (M. R.), quoted above, lends some support to that view.

Chemical Findings.

The blood chemistry has been investigated in five severe cases of coeliac infantilism which have been under my observation in the course of the last two or three years. In four cases the blood calcium was low before light treatment was started, but rose under treatment, and in these cases there was also at some period a low blood phosphorus. In the remaining case (M. C.), a child who did not show active rickets, the blood calcium just reached the lower limit of the normal (9·0 mg. per cent.), and the phosphorus was 5·65 mg. per cent. The blood findings are, therefore, quite consistent with the view that the bone deformities are rachitic in origin. The occurrence of tetany as a complication of coeliac disease is also exactly what would be expected in view of the low values obtained for blood calcium.

Recently we have attempted to obtain an indication of the Ca-ion concentration of the blood serum by the method of ultra-filtration through collodion sacs under moderate pressure as described by Pincus, Peterson and Kramer[16]. The sacs used were prepared from an eight per cent. solution of Schering's celloidin in equal parts of alcohol and ether. A fresh sac was used for each estimation, 2 cc. of serum being placed in the cell and a negative pressure of 120–125 mm. Hg. maintained for four hours. At the end of this time the calcium was estimated both in the ultra-filtrate and in the residual serum. The sum of the estimations of calcium inside and outside the cell was found to be the same as the total calcium with usually a less error than one to two per cent. Pincus and his co-workers assume that the calcium in the filtrate is ionised and they refer to this as "free calcium"; and they regard the calcium which does not filter as bound to protein and practically un-ionised, and this portion they refer to as "bound calcium." They found that the

" free calcium " normally amounts to 50 or 60 per cent. of the total calcium, but that in tetany the " free calcium " may be diminished to 40 or 30 per cent. of this amount or even less.

The number of observations made by this method has not been very large but has included estimations in cases of tetany, coeliac and renal rickets, nephrosis, pink disease, and thrombocytopenic purpura. The blood-calcium figures vary so much in such a series of cases that it would appear better to express the " free calcium " in mg. per cent. rather than as a percentage of the total calcium. The results obtained on the whole have shown somewhat smaller values for " free calcium " than those obtained by Pincus, but they confirm his statement that in tetany the amount of " free calcium " is greatly diminished. In tetany it is apparently always less than 2.5 and usually less than 2·2 mg. per cent. Two cases of coeliac rickets, both of whom had suffered from frequent attacks of tetany, showed a low " free calcium " (2·2 and 2·5 mg. per cent.) although at the time of these observations both were free from active rickets ; whereas in the two other cases of coeliac disease, neither of which had been complicated by rickets or tetany, it was 3·2 and 3·9 mg. per cent. respectively (see Table I). Lathrop[17], writing on renal rickets, refers to a figure of 3·8 mg. per cent. as being normal, and in my normal cases the free calcium in nephrosis was 3·2, in pink disease 3·8, and in thrombocytopenic purpura 3·9 mg. per cent.

These observations therefore, although admittedly they are but few in number, support the suggestion that Ca-ion concentration is low in coeliac rickets, and that the bone changes are truly rachitic.

A complete record of the blood chemistry findings and also of the results of examination of the stools is shown in Table I.

TABLE I.

Treatment.

The fact that rickets may arise and develop progressively in a child while under treatment for coeliac disease was forcibly brought home to me in the case of a girl (M. R.) who developed coeliac disease in September, 1919, when she was five years old. She was placed on a fat-free dietary and given bile salts by the mouth, with the result that considerable improvement occurred ; but in January, 1921, she developed the first of several attacks of tetany, and in May, 1922, genu valgum was noticed. From this time onwards, in spite of splinting, the deformity increased, and eventually in 1923, although her general condition had improved, walking became impossible. Radiograms (Fig. 6) taken in March, 1925, showed the changes already described as occurring in a case of moderate severity. Since the bone changes were apparently rachitic and progressive in character, it was decided to try the effect on them of ultra-violet irradiation. After two months of treatment it was obvious that healing had commenced and Dr. Teall reported as follows : " The bone condition appears to be improving, new bone is being laid down at the end of the metaphysis much as in healing rickets " (Fig. 7). The treatment was continued and healing slowly progressed until by the end of the year the rickets had completely healed and the child had begun to walk again. During

TABLE I.

Case.	Date.	Total Fat: % of Dried Fæces.	Distribution of Fat expressed as percentage of Dried Fæces.				Blood serum.			Comments.
			Unsaponified.	Saponified.	Free Fatty Acid.	Neutral Fat.	Total Calcium, mg. %	Free Calcium, mg. %	Phosphorus, mg. %	
M. R., Female, Born 1919.	4/3/25	18·7	2·4	16·3	2·4	0·0				Fat free diet. Active rickets, tetany. Ultra-violet irradiation commenced.
	7/3/25	15·7	1·8	13·9	1·8	0·0				
	20/10/25						8·4		4·4	
	17/3/27						10·0	2·5	5·0	No active rickets for one year.
D. P., Female, Born 1916.	/2/26						7·5			Tetany, slight rickets.
	26/3/26	58·1	14·0	44·1						Ordinary diet, then placed on fat free diet, ultra-violet light and irradiated cholesterol.
	24/9/26	28·6	7·6	21·0						
	1/15/26						7·4		3·9	Rickets healed (X-ray).
	26/10/26						9·1		3·7	
	9/3/27						8·6	2·3		Had not attended Hospital since October 1926, and had discontinued all treatment.
B. D., Male, Born 1915.	9/9/25	55·9	21·0	34·9	12·6	8·4				Ordinary diet, severe rickets. Ultra-violet irradiation commenced.
	21/9/25						6·0		5·8	
	21/11/25	21·3	13·3	18·0	6·2	7·1				Fat free diet.
	22/6/26	25·5	9·2	16·3	4·0	5·2				Irradiated cholesterol since 27/12/25.
	29/10/26	18·6	3·1	15·5			9·3		3·4	Carbohydrates increased and no ultra-violet light since 14/6/26, but irradiated cholesterol continued.
	23/3/27	28·0	18·0	10·0	12·2	5·8			4·35	Has received ultra-violet light and irradiated cholesterol since 29/10/24.
	23/4/27						10·5			Rickets healed.

Table: Showing results of blood chemistry and amount and distribution of fat in the stools.

TABLE I (*contd*).

Case.	Date.	Total Fat: % of Dried Fæces.	Distribution of Fat expressed as percentage of Dried Fæces.				Blood serum.			Comments.
			Unsaponified.	Saponified.	Free Fatty Acid.	Neutral Fat.	Total Calcium, mg. %	Free Calcium, mg. %	Phosphorus, mg. %	
M. C., Female, Born 1922.	15/10/26	42·1	31·7	10·4	17·3	14·4				Ordinary diet. Osteoporosis, no rickets.
	28/10/26						9·0		5·65	Fat free dietary.
	15/12/26	13·1	3·6	9·5	2·9	0·7				
	5/1/27	9·2	2·5	6·7	0·4	2·1				
	17/3/27						11·6	3·92	4·43	Received ultra-violet light and irradiated cholesterol since October 1926.
O. A., Female, Born 1922.	25/2/25	14·2	1·9	12·3	1·2	0·7				Fat free dietary, no rickets.
	7/3/25	13·7	2·9	10·8	2·9					
	22 to 28/3/25	8·1	1·3	6·8						Average of five days. During this time the diet was skimmed milk (Trufood) and Casec. The average fat intake per day 7·74 g. and average fat in fæces 0·41 g., giving a fat absorption of 94·7 per cent.
	25/9/25	42·2	6·5	35·7			6·0		5·8	
	16/10/25								3·31	Irradiated cholesterol started.
	1/12/25	35·9	17·3	18·6	14·7	3·6				
	30/6/26	19·6	5·9	13·7	3·1	2·8				
	26/10/26						9·6		4·85	
	4/1/27	16·0	3·5	12·5	0·2	3·3				
	18/2/27						11·9	3·2	4·4	

the year 1926 the treatment was continued and at the present time the child, although somewhat stunted in growth, looks well and has grown considerably. She is on normal diet, attends school, and can run and hold her own in play with other children. The knock knee is decidedly less marked than when treatment was first instituted in March, 1925 (see Figs. 8–14).

Even more striking have been the results of treatment in the case of B. D., whose clinical condition and radiograms on admission to hospital have already been described in detail (Fig. 4). This boy developed *diarrhœa alba* at three years of age, and when six years old was put into splints for knock knee. At eight years of age he had an attack of influenza followed by tetany and since that time had been unable to walk. He had apparently not been treated for coeliac disease before his admission to hospital at the age of ten and a half years, in August, 1925. He was given ultra-violet light treatment for two months from August to October, 1925, without the diet being modified in any way. A very slight but definite increase in calcification occurred during that time (Figs. 15–16). On October 12th he was given a " fat free " diet and the amount of carbohydrate food limited. During the next two months improvement continued and increased so that at the end of December some of the fractures had healed (Fig. 17) ; the rate of improvement was, however, slow, and in view of the good results obtained by giving irradiated cholesterol in ordinary rickets it was thought advisable to try it in this case. As liquid paraffin is unabsorbed by the intestine an attempt was made to use this as a vehicle, and the administration of a 2% solution of irradiated cholesterol in paraffin was therefore started on December 3rd, 1925, three drams of this solution being given three times a day. The child stood this well for a time but eventually the paraffin appeared to cause looseness of the bowels and from that time onwards the cholesterol was administered in powder form with the meals. After the addition of cholesterol the rate of recovery, although still slow, increased and was continuous (Figs. 18–19). On June 19th, 1926, he was discharged from hospital to his home. At this time his diet was relaxed somewhat as far as carbohydrates were concerned and ultra-violet light treatment was stopped, but the adminstration of irradiated cholesterol was continued and a radiogram taken on August 12th (Fig. 20) showed that he was steadily improving. He was seen again on October 28th, 1926, when as will be seen from the radiogram (Fig. 21) the degree of healing of the bones was most marked. From this date until the present time he has been receiving ultra-violet light treatment as well as irradiated cholesterol and a radiogram (Fig. 22) taken on March 23rd, 1927, shows that the bones are practically healed. He first attempted to stand about April, 1926, and on his discharge from hospital in June he was able to walk a step or two with support. In October he was able to walk unaided and now he walks well, rides a tricycle one mile to school and has grown 1½ inches since treatment was first instituted. One or two other points of interest in this case may also be mentioned. During the time he was in hospital he had repeated attacks of bronchitis, but since October this liability appears to have completely disappeared and at the same time his thorax, which at the time of his admission to hospital appeared small

and shrunken, has expanded and the rickety rosary which was such a conspicuous feature is very much less noticeable. Again, for some three or four years before he came under my care his hair had become harsh and grew but slowly, so that it needed cutting only about once in every eighteen months. The first indication of recovery noticed by the parents was that his hair became smooth and began to grow so that it was necessary to have it cut. The hair is now normal in texture and growth.

The advantage that ultra-violet light possesses over heliotherapy in the treatment of these cases, at least in the industrial areas of the Midlands, was well demonstrated in the foregoing case. Previous to his admission to the Children's Hospital this boy had received a thorough course of heliotherapy in a country hospital near Birmingham and was so pigmented that when I first saw him I thought he was a coloured child, but radiograms taken at that time (Fig. 4) showed no sign of healing.

In every case investigated the concentration of the blood phosphorus and calcium has increased during the process of treatment.

Finally, I would stress one other point in treatment, namely, the length of time required to effect a cure of rickets. In the first case to which I have referred, nine months of light treatment was required, and in the other eighteen months ; periods which contrast markedly with the time required for the cure of ordinary rickets.

There does not, therefore, appear to be any doubt but that the bone deformities of coeliac infantilism, even when of the most extreme degree, can be cured by exposure to ultra-violet light or by the adminstration of irradiated cholesterol, also that this can occur even when the patient is on a " fat-free " dietary and while the coeliac disease is still active. Further, I believe that by adopting this method of treatment in coeliac disease the onset of rickets can be prevented and it, therefore, now forms part of the routine treatment in cases which come under my observation.* One such case, aged four and a quarter years, has been under treatment for coeliac disease for three years, and during the last fifteen months of this period she has been receiving ultra-violet light treatment and irradiated cholesterol. Radiograms of her bones taken recently show a bone that is in my opinion far less atrophic than is usual in cases of this age, one indeed that can be regarded as almost normal for a child of her size. The value of ultra-violet light in the treatment of coeliac disease has been recently pointed out by Michelmore[18], but no reference was made to its effect on bone. The fact that cure does occur under light treatment is additional evidence that the bone deformities are of rachitic origin, but the necessity for such long periods of treatment before a cure is obtained is proof that the condition is not simple uncomplicated rickets.

I would therefore submit that the evidence produced, namely, (1) the result of X-ray examination, (2) the blood calcium and phosphorus values, (3) the clinical characteristics, (4) the occurrence of tetany and (5) the results

* Irradiated ergosterol, made up with a chocolate basis, has now been substituted for irradiated cholesterol in the routine treatment of coeliac disease.

of treatment by ultra-violet light and irradiated cholesterol, constitutes a convincing proof that the bony changes in coeliac infantilism are rachitic in origin.

In Part I of this paper I pointed out that the bone deformities of renal infantilism were those of true low-calcium rickets. In coeliac disease also, although the blood phosphorus is low, the deformities signify low-calcium rickets, and this is the explanation of the frequent occurrence of tetany in association with coeliac rickets. The development of rickets in coeliac infantilism is due primarily to the deficient absorption of fat and therefore of Vitamin D, calcium and phosphorus. This defect of absorption is probably also the cause of the poorly calcified atrophic and osteoporotic bone seen before rickets appears ; indeed in a case of this type McCrudden and Fales[2] actually found a negative calcium balance. Although in such a bone rickets is not manifest, yet the bone is potentially a rachitic one and only awaiting a period of growth actually to declare itself.

I have great pleasure in expressing once again my indebtedness to my colleagues Dr. C. G. Teall, Radiographer, and Dr. E. M. Hickmans, Biochemist to the Children's Hospital, Birmingham, for their help in the preparation of this paper, and to the Medical Research Council for defraying part of the expenses of the investigations.

Conclusions.

1. The bone deformities of coeliac infantilism are rachitic in nature. Although the blood phosphorus is low the rickets is of the low calcium type ; which is the explanation of the frequent occurrence of tetany.

2. The evidence that the bone deformities are rachitic is based on : (*a*) the clinical characters, (*b*) the results of blood examinations, (*c*) the radiogram, and (*d*) the result of treatment by ultra-violet light and irradiated cholesterol.

3. The cause of coeliac rickets is to be found in defective fat absorption, with resultant defective absorption of Vitamin D, calcium and phosphorus.

4. The osteoporotic bone is a stage in the development of active rickets.

5. Growth is an important factor in the development of the bone deformities.

6. Coeliac rickets can be completely cured, even when the patient is on a fat-free dietary, by ultra-violet light irradiation and/or the administration of irradiated cholesterol.

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LIST OF ILLUSTRATIONS.

Figs. 1–4.—A series of radiograms showing the probable stages in the development of the severest form of coeliac rickets. All these radiograms show delay in the appearance of centres of ossification.

Fig. 1.—Radiogram (taken 23/10/26, of M. C., born 1922) showing the atrophic and osteoporotic character of the bones, the thin cortex, fragile trabeculæ but sharp epiphyseal line of the pre-rachitic stage.

Fig. 2.—Radiogram (taken February 1926, of D. P., born 1916) showing the earliest signs of rickets. The lower ends of the radius and ulna are slightly enlarged, the spongy tissue is more open and there is slight rachitic irregularity of the epiphyseal line. There is a fracture of the shaft of the ulna.

Fig. 3.—Radiogram (taken 10/3/25, of M R., born 1919) showing the moderately severe stage of coeliac rickets. The bones are atrophic and show osteoporosis. The cortex is thin, there is an open and delicate trabecular mesh work and a well marked rachitic metaphysis.

Fig. 4.—Radiogram (taken 12/8/25, of B. D., born 1915) showing the severest type of coeliac rickets. The bones show extreme osteoporosis particularly manifest in the metacarpals and phalanges, and there are multiple fractures of the ulna and radius. The rachitic metaphysis is not obvious, the picture being that of the " passive type " of rickets.

Fig. 5.—Radiogram from a severe case of uncomplicated rickets in a child aged 2½ years. This radiogram shows a marked similarity to the radiogram of severe cœliac rickets shown in Fig. 4.

Figs. 6–12.—A series of radiograms showing stages in the complete cure of a case (M. R.) of moderately severe coeliac rickets. The dates on which the various radiograms were taken are as follows: Fig. 6, 10/3/25; Fig. 7, 25/5/25; Fig. 8, 21/7/25; Fig. 9, 21/10/25; Fig. 10, 8/12/25; Fig. 11, 14/4/26 and Fig. 12, 24/1/27.

Fig. 13.—Radiogram of lower end of femur and upper ends of tibia and fibula of M. R., taken 10.3.25, showing osteoporosis and rickets with some indication of transverse striations.

Fig. 14.—Radiogram of M. R., taken 14/4/26, for comparison with Fig. 13. The rickets is now healed and well marked transverse striations have formed.

Figs. 15–22.—A series of radiograms showing the stages in the complete cure of a case of severe coeliac rickets (B. D.). The dates in which these radiograms were taken are as follows: Fig. 15, 18/8/25; Fig. 16, 13/10/25; Fig. 17, 23/12/25; Fig. 18, 24/3/26; Fig. 19, 8/6/26; Fig. 20, 12/8/26; Fig. 21, 28/10/26; Fig. 22, 23/3/27.

Ultra-violet irradiation was commenced on 18/8/25, continued until 19/6/26, and restarted on 28/10/26. The diet was " fat free " from 13/10/25; from 23/12/25 irradiated cholesterol was given.

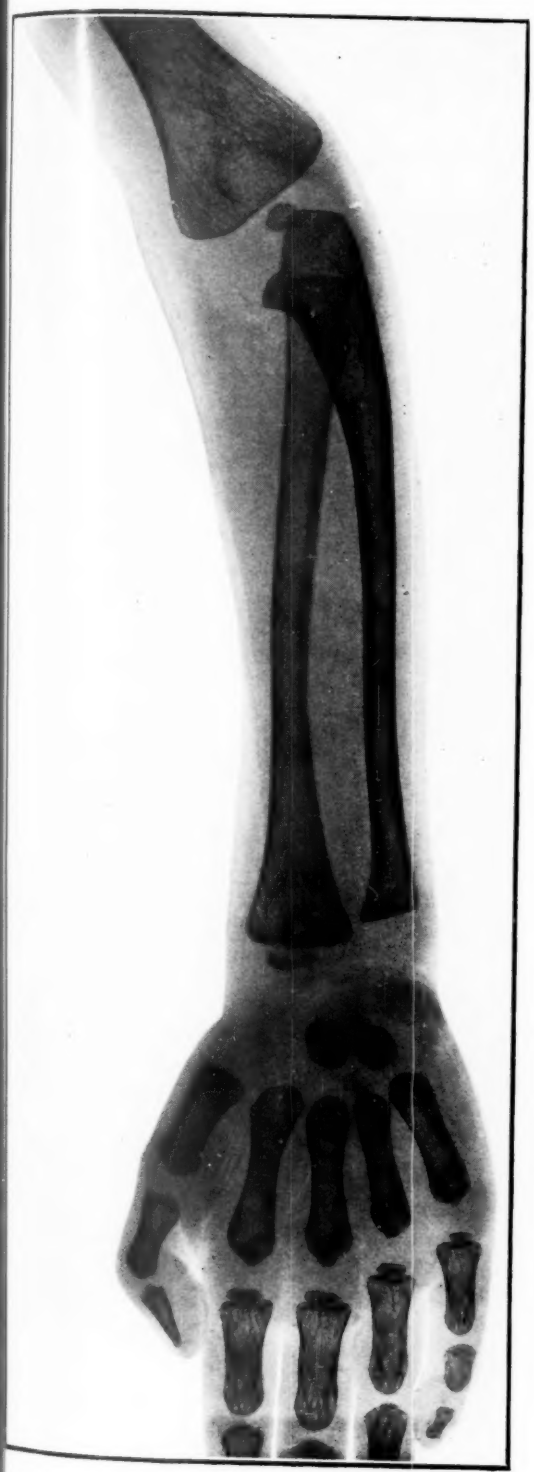

Fig. 1.

Fig. 2.

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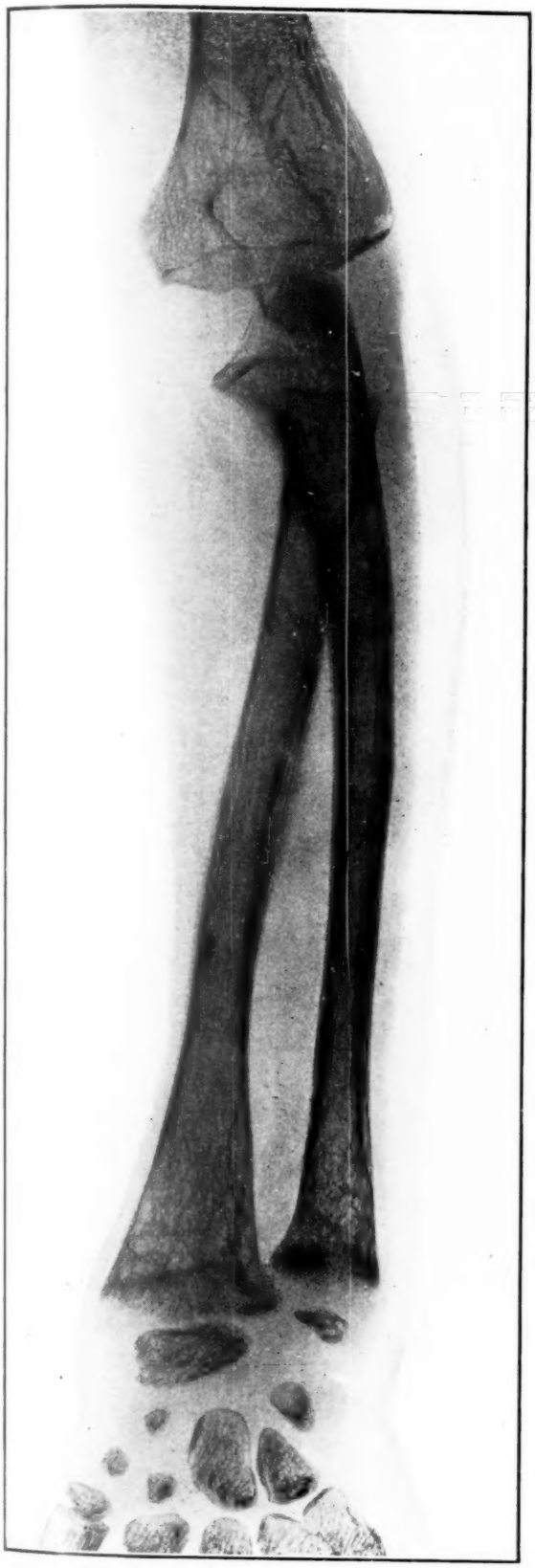

Fig. 3.

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Fig. 5.

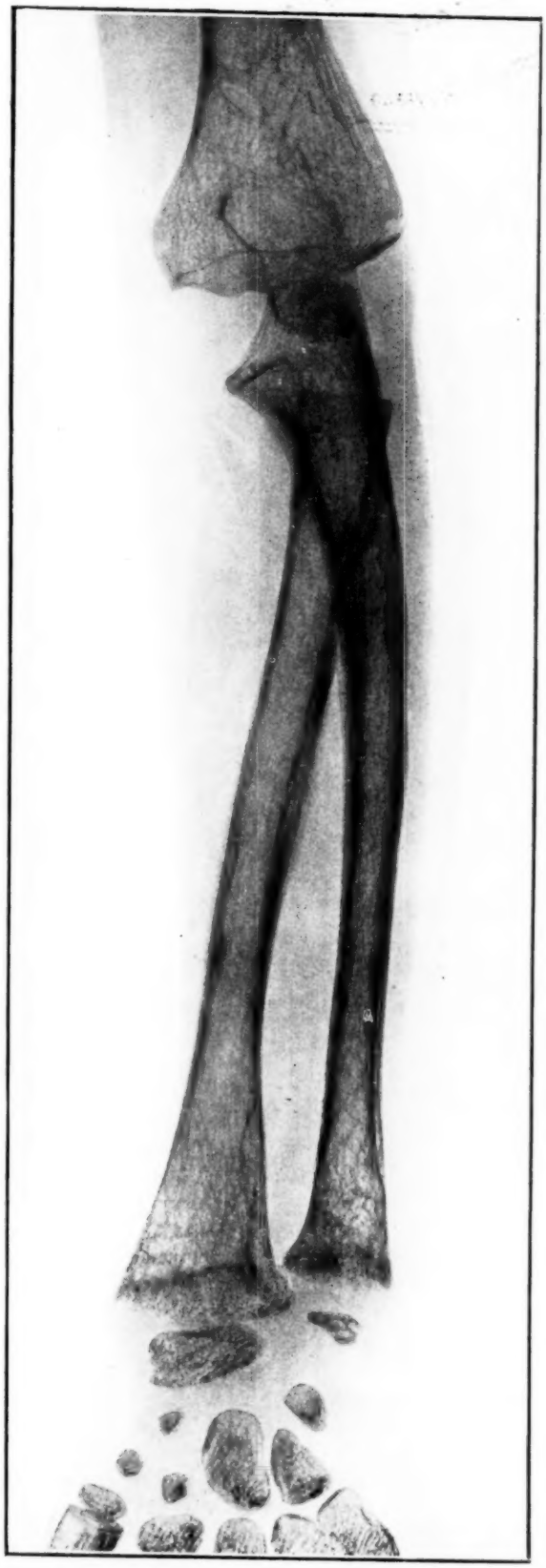

Fig. 6.

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Fig. 7.

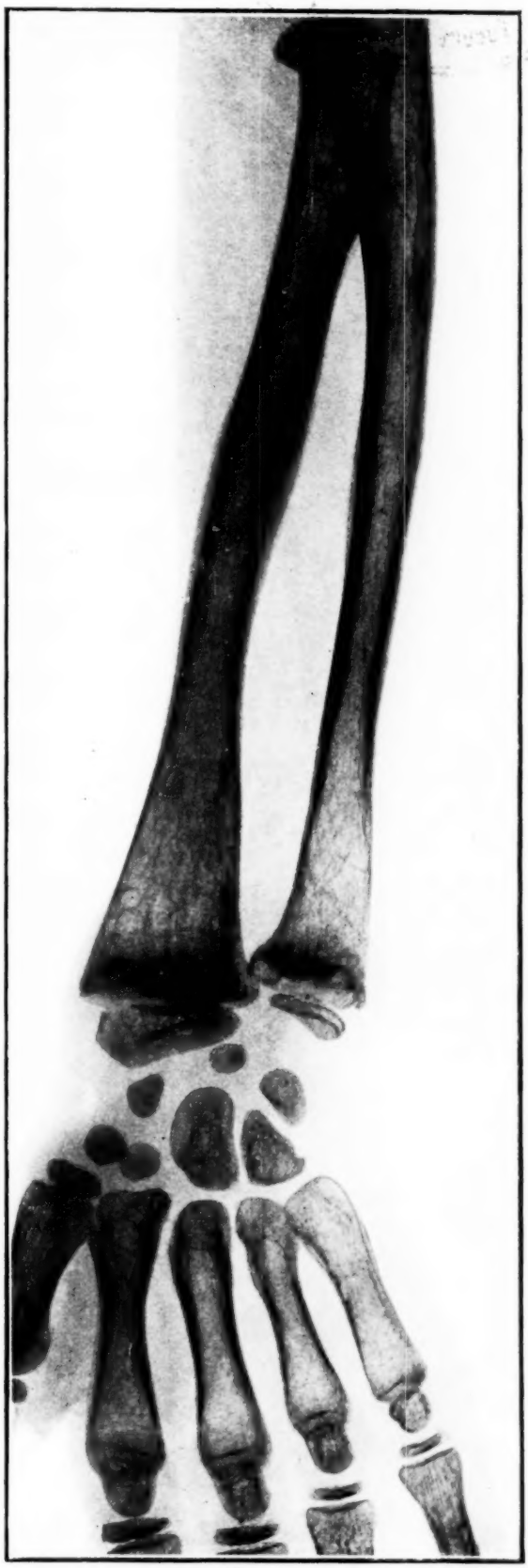

Fig. 8.

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Fig. 9.

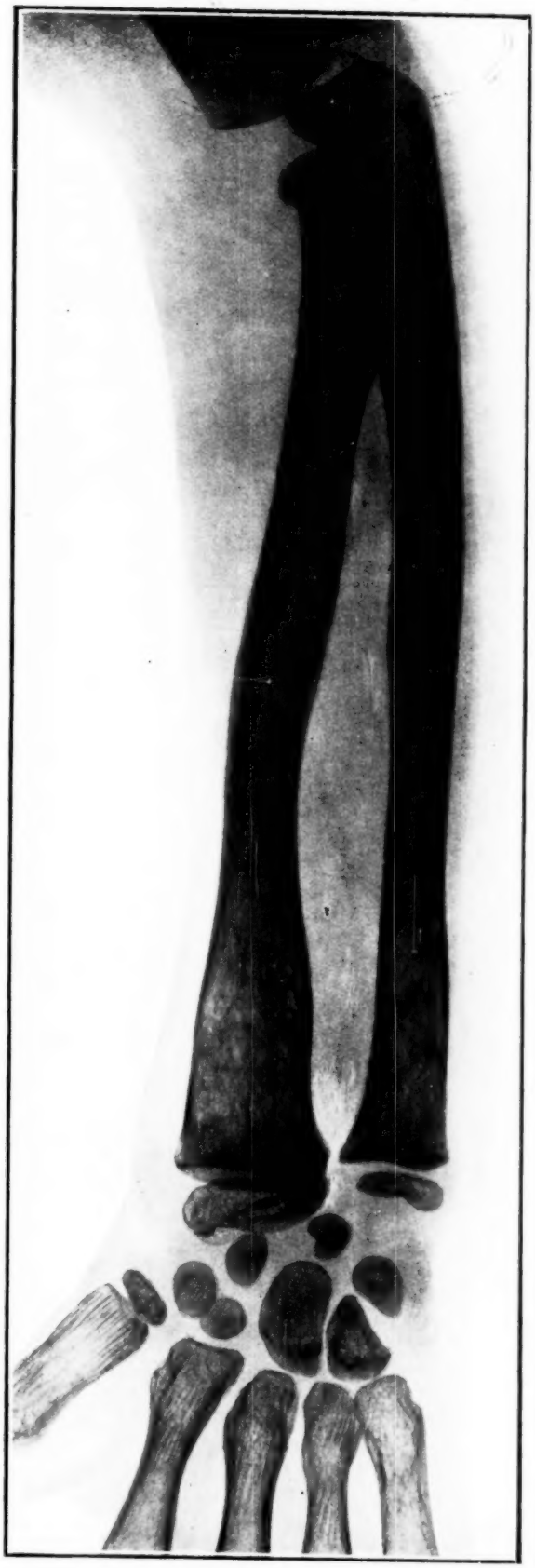

Fig. 10.

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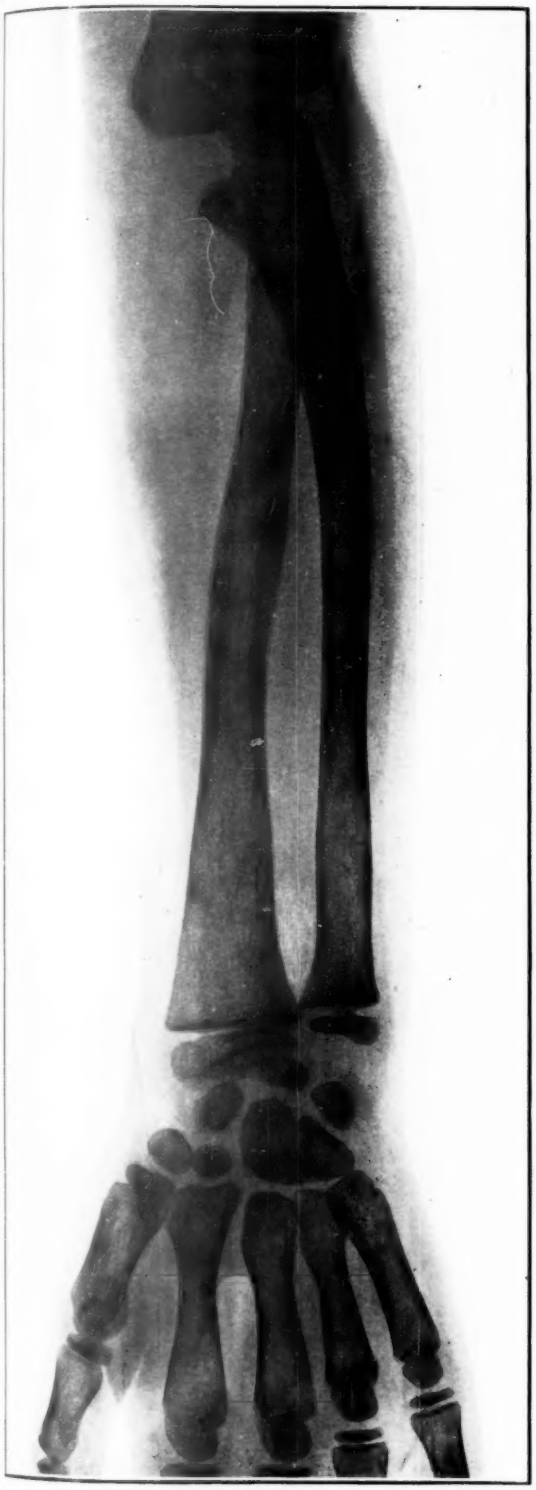

Fig. 11.

Fig. 12.

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Fig. 13.

Fig. 14.

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Fig. 15.

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Fig. 17.

Fig. 18.

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Fig. 19.

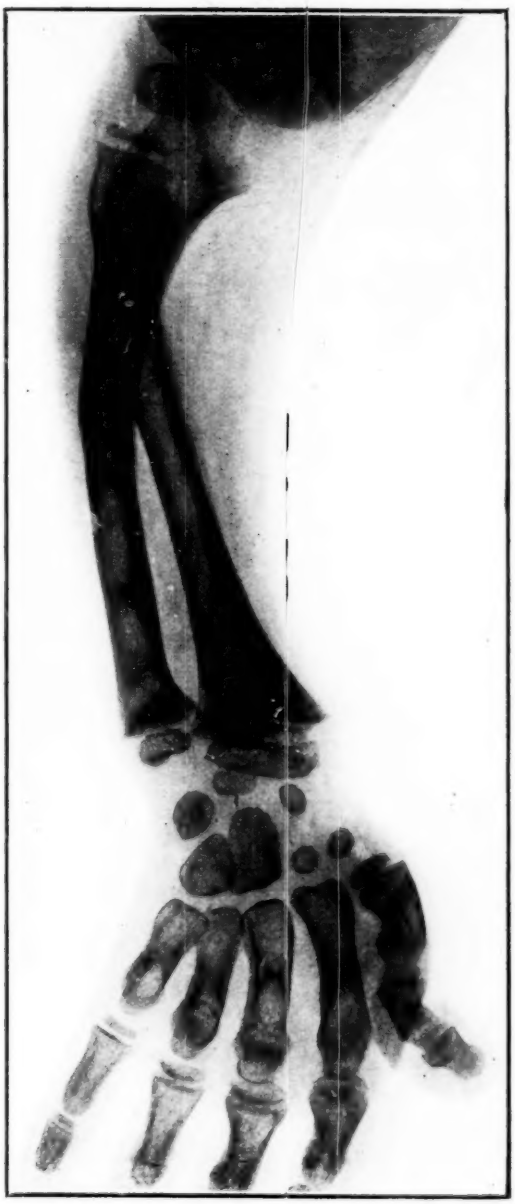

Fig. 20.

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Fig. 21.

Fig. 22.

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OBSERVATIONS ON THE ACTION OF ACETONE.

BY

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Ever since it has been shown that diabetic coma is associated with a marked acetonuria and acetonæmia, it has been suggested that the presence of acetone is the *fons et origo* of the symptoms of coma. Kussmaul[1] first investigated the pharmacological action of acetone experimentally on man, but with oral doses amounting to six grams he obtained no results. Using rabbits he found that the subcutaneous injections of acetone led to symptoms of intoxication and stupor, the action being less than that of chloroform or ether but stronger than alcohol. The symptoms were even more marked if the acetone was inhaled, and resembled clinically the coma of diabetes. Kussmaul accordingly concluded with the earlier workers that acetone was the direct cause of diabetic coma. Frerichs[2] gave large doses to men and dogs but without any special results and decided that acetone *per se* was not the cause of the coma. Penzoldt[3], however, as the result of his experiments on rabbits maintained that the acetone played an important role though it was not the only cause. Tappeiner[4] studied the effect of acetone inhalations on dogs and rabbits, and described two stages of acetone poisoning: first, a stage in which the blood pressure is raised with an increase in the pulse and respiration rates, and secondly, a stage of depression associated with a lowering of blood pressure, a decrease in the pulse and respiration rates and a gradual abolition of reflex activity. The second stage was marked by a steady fall in the temperature of the body until death ensued from respiratory failure. Prolonged inhalation of large amounts of acetone was required to produce the second stage. Albertoni [5] in a long series of experiments on dogs found that oral administration of acetone in doses amounting to 5 grams per kilo produced at most a slight fall in the systolic blood pressure, while on man the only effect to be observed was a slight narcosis. He also produced albuminuria in dogs with these large doses. Rhamy[6] stated that subcutaneous injections of acetone in guinea-pigs were more toxic than those of methyl alcohol. Hewlett[7], on the other hand, maintained that the toxicity of acetone was very low. Salant and Kleitman[8], as a result of their experimental work concluded that acetone possesses a double action causing both depression and stimulation, but chiefly the former. They drew attention to the fact that although the amount of acetone present in the blood in acidosis is comparatively small, yet the tissues and the organs are exposed to its action for a relatively long period, and they inclined to the view that acetone *per se* is the cause of the symptoms in diabetic coma.

Allen and Wishart[9] have shown that young fasting animals and animals that have been phlorhizinised or depancreatised (in other words, suffering from

carbohydrate starvation) are rendered more susceptible to the injection of acetone bodies. They also found that a hyperglycæmia resulted from the injection of acetone and the neutral salts of keto-acids.

In view of the varying experimental results the effect of acetone was considered worthy of further investigation.

Effect of Acetone on the Nervous System.

This effect was studied on rabbits and some of the results are recorded in Table 1. A 20% solution of acetone was injected intravenously, into the veins of the ear. In each case there was an interval of 24 hours between the injections to prevent cumulative action. Doses below 0.8 c.cm. pure acetone per kilo of body weight had no apparent effect on the animal. When, however, this dose was exceeded, it was found that the animals become stuporous and lay unconscious for a short period, usually 1 to 3 minutes. Recovery was fairly rapid and usually complete within three minutes. With very large doses convulsions were observed. These were clonic in type and lasted for much less than half the total period of unconsciousness. Reflexes were invariably abolished during the period of complete unconsciousness. The respirations during the period of coma were usually more rapid. The severity and duration of the symptoms were increased by increasing the dose of acetone, but not always proportionately. The rate of injection within limits (1 to 5 minutes) had no effect on the duration or severity of the symptoms produced.

TABLE I.

Number.	Weight of Rabbit in Kilos.	Acetone per Kilo. cc.	Reaction.
1	1·5	0·4	Nil.
	1·5	0·6	Nil.
22	1·3	0·8	Nil.
1	1·5	1·0	Unconscious for 30 sec. Recovery period 10 sec.
18	1·9	1·0	Unconscious for 75 sec. Recovery rapid.
4	1·1	1·2	Unconscious for 30 sec. Recovery period 60 sec.
	1·1	1·2	Same result. This dose given 10 min. after previous one.
1	1·5	1·3	Unconscious for 60 sec. Recovery period 10 sec.
4	1·1	2·4	Convulsions for 2½ min. Respiration rapid. Nystagmus. Regained balance in 8 min. Still dazed at end of 17 min.

The effects of Intravenous Injections of 20% Acetone Solution.

Hirschfeld[10], in 1895, pointed out that the presence of carbohydrates prevented the formation of acetone bodies and Shaffer[11], in 1921, showed that the oxidation of acetone was greatly accelerated by the presence of glucose. Geelmuyden[12] has also suggested that a combination of acetone bodies and

carbohydrate was necessary before the former could be oxidised. In order to test if glucose was able to prevent or minimise the toxic symptoms, a 10% solution of glucose was injected simultaneously with the acetone. In every case the period of unconsciousness was shortened and in two cases the occurrence of convulsions was prevented. In some experiments glucose was also injected 5 minutes before the acetone and invariably there resulted not only shortening of the duration of the reaction but a diminished intensity of the toxic effects on the nervous system.

The value of alkali in the treatment of ketosis has long been known and until recently occupied a prominent place in the treatment of diabetic coma. In a series of experiments in which the acetone was injected along with 6% sodium bicarbonate solution, the effect observed was similar to that of the simultaneous injection of glucose. When, however, the sodium bicarbonate solution was administered before the acetone, its preventive action was much stronger than that of glucose.

These results are tabulated in Tables II and III. In one case, the same amount of saline was injected previously instead of glucose or bicarbonate solution in order to rule out the possible effect of the fluid *per se*.

TABLE II.

Number of Animal.	Weight in Kilos.	Acetone per Kilo. cc.	Remarks.	Reaction.
1	1·5	1·3		Unconscious 30 sec. Recovery period 10 secs.
		1·3	8 cc. 20% glucose soln. simultaneously.	Nil.
2	2·0	1·2		Unconscious 3 mins. Recovery period 2 mins.
		1·2	10 cc. 20% glucose soln. simultaneously.	Dazed 10 sec.
		1·2	10 cc. 40% glucose soln. simultaneously.	Dazed 10 sec.
		1·2	10 cc. 6% $NaHCO_3$ soln. simultaneously.	Unconscious 30 sec. Recovery period 2 min.
3	1·2	1·2		Convulsion. Unconscious for 3 min. Recovery period 3 min.
		1·2	6 cc. 20% glucose simultaneously.	Unconscious 30 sec. Recovery period 2½ mins.
		1·2	6 cc. 6% $NaHCO_3$ simultaneously.	Unconscious 20 sec. Recovery 40 sec.

The effect of Injections of Acetone modified by simultaneous injections of Glucose or Sodium Bicarbonate.

Effect of Acetone on the Respiration.

As a general rule the effect of acetone on the breathing was an increase in both rate and depth. Occasionally, this increase in minute volume was preceded by a short period of apnœa. In rabbits, the respiratory rate and depth were always increased, leading in one case to an increase in minute volume of 340%. In cats, there was occasionally observed a very slight depression of the respiratory rate together with a decrease in the depth of the individual

respirations. Repeated doses produced no increase of effect in rabbits but in cats the period of apnœa was greatly prolonged. Both in cats and rabbits, the effect very soon passed off although the blood contained a very large amount of acetone (303 mgm. % in one case).

TABLE III.

Number of Rabbit.	Weight in Kilos.	Acetone per Kilo cc.	Remarks.	Reaction.
18	1·9	1·0		Unconscious 75 secs.
		1·0	10 cc. 10% glucose 5 min. previously.	,, 15 ,,
		1·0	10 cc. 6% $NaHCO_3$ 5 mins. previously.	,, 5 ,,
20	1·8	1·0		Unconscious 90 secs.
		1·0	10 cc. 10% glucose 5 min. previously.	,, 20 ,,
		1·0	10 cc. 6% $NaHCO_3$ 5 min. previously.	,, 5 ,,
21	1·4	1·0		Unconscious 75 sec.
		1·0	10 cc. 10% glucose 5 mins. previously.	,, 50 ,,
		1·0	10 cc. 6% $NaHCO_3$ 5 mins. previously.	,, 30 ,,
		1·0	10 cc. 0·9% NaCl 5 mins. previously.	,, 70 ,,
23	1·4	1·0		Unconscious 70 sec.
		1·0	10 cc. 6% $NaHCO_3$ 5 mins. previously.	,, 25 ,,
		1·0	10 cc. 10% glucose 5 min. previously.	,, 50 ,,

The effect of injections of Acetone modified by previous injections of Glucose or Sodium Bicarbonate.

Injection of either glucose or bicarbonate along with the acetone did not alter the effect of the acetone on the respiration, nor was the previous injection of these substances more efficient. With lethal doses, respiratory failure took place some minutes before the heart ceased to beat, thus confirming the observation of Salant and Kleitman[8].

Effect of Acetone on the Circulation.

In all cases acetone injections led to a fall in the blood pressure unless the injection was very slow when practically no effect was observed. On one or two occasions a slight rise preceded the fall. Previous injections of glucose seemed occasionally to lessen the fall. The rate of recovery depended for the most part on the period of apnœa. The recommencement of the respiratory movements was usually accompanied by a fairly sharp rise in the blood pressure. Administration of suprarenal extract was more than sufficient to counteract the fall of blood pressure due to the acetone.

Excretion of Acetone.

In all cases, irrespective of the dose, acetone was excreted within twenty hours of its administration, the complete excretion being determined by its disappearance from the urine. One fact of interest may here be noted, viz., that within half an hour of the administration of a large dose of acetone, the blood-acetone bodies were not nearly as high as might have been expected. For example, in one case where 14·5 cc. of 20% acetone were injected, the blood should have contained 2·9 cc. acetone if none had been excreted. The total acetone bodies were determined on a sample of blood taken approximately 5 minutes after the injection and were found to be 0·303%. Taking the blood-volume as one-thirteenth of the body weight, this represents only 0·56 grms.—roughly one-fifth of the amount injected. The urine at this time was free of acetone and as there was no perceptible odour of acetone in the breath, it seems unlikely that the other 4/5ths, or 2·3 grms., were excreted by the lungs. This suggests that the acetone was dealt with by the tissues in some way.

Effect of Acetone on the Blood Sugar.

Some observations were also made on the effect of acetone on the blood sugar. The animals were in all cases starved for twenty-four hours and the fasting blood sugar estimated. Results were neglected unless the fasting blood sugar value was between 0·100 and 0·125%. The acetone was injected into the ear veins and the blood was taken from these veins at intervals after the injection. The results are given in Table IV.

TABLE IV.

Number.	Weight of Animal.	Acetone per kilo cc.	Fasting Blood Sugar.	Blood Sugar at end of—				
				5 min.	15 min.	30 min.	45 min.	60 min.
4	1·1	1·2	·115	·154	·166	—	—	—
5	1·05	1·2	·119	·113	·118	·113	—	—
8	2·15	1·0	·107	·110	·139	·106	·108	·100
9	1.4	0·5	·125	·111	·169	·164	·149	—
10	1.2	0·3	·117	·128	·156	—	·119	—
11	2.15	water	·117	·127	·117	·117	·109	—

The effect of Injections of Acetone on the fasting Blood Sugar.

In every case except one there is a slight rise in the blood sugar following the injection of acetone. The rise in the blood sugar is not directly proportionate to the dose of acetone—in fact the smaller doses gave the greater rise. It is quite conceivable that if the dose of acetone is large enough to produce convulsions, no rise in the blood sugar would occur, because it has been definitely shown that convulsions themselves will cause a fall in the blood sugar.

In no case did the rise in blood sugar lead to a glycosuria. The presence of glycosuria following the injections of acetone has been recorded by von Jaksch [13]

and others. Von Noorden[14] also states that hyperglycæmia and glycosuria occur after the administration of acetone and seems to be quite definite in his contention that this condition is the result of deficiency of oxygen. In none of our experiments was there ever a hyperglycæmia great enough to cause a suspicion of a glycosuria even when taken at the end of an apnœic period. It seems to us that the slight rise cannot be attributed to defective oxidation of the blood, although the possibility still remains that acetone inhibits the oxidation processes in the cells.

Effect of Acetone on the CO_2-Content and the CO_2-Combining Power of the Blood.

In two cases the total CO_2-content of the arterial blood was determined as well as three points on the CO_2-dissociation curve. For ready comparison Table V shows the volumes per cent. of CO_2 taken up by the blood when exposed to tensions of CO_2 of 20, 40 and 60 mm. before and after the intravenous administration of 10 cc. of 20% acetone to cats.

TABLE V.

	Volumes of CO_2% taken up at—			CO_2-content of Arterial Blood.	*p*H.
	20 mm.	40 mm.	60 mm.		
Cat. 1.—Before ...	33·5	47·0	54·5	54·6	7·20
After	31·8	45·8	52·3	53·8	7·15
Cat. 2.—Before ...	36·5	48·5	56·0	44·6	7·38
After	31·5	44·5	51·2	45·0	7·31

It will be seen that in each case there is a slight decrease in the CO_2-combining power, that is, the curve is shifted slightly to the right, although in the first case the difference is probably almost within the limits of experimental error. The *p*H values before and after the injections were worked out from the information obtained above by means of the arterial point on the dissociation curve and the application of Hasselbalch's equation. These figures are also given in Table V. In each case there is a definite fall in the *p*H indicating an acid-poisoning effect of the acetone. Apropos of the low initial *p*H of the blood of Cat 1, it should be mentioned that in each case the animal was under the influence of urethane, which may have accounted for the low figure recorded before the injection.

Discussion.

The results of acetone injection show a close resemblance to those produced by acid poisoning. The same effect on respiration and circulation have been described as occurring after injections of acids such as phosphoric acid or hydrochloric acid by Mathison[15]. It is an old observation that both oral and intravenous administration of acids leads to glycosuria[16]. This close similarity in effects leads us to think that the symptoms of acetone poisoning may be due, in part at least, to acid-poisoning of the blood. It may be argued

that this change in acid-base equilibrium is secondary to the effect on respiration as produced by the action on the respiratory centre. In some of the experiments, however, the effect on the blood sugar occurred without any change in the nervous activity. As a matter of fact, the most pronounced rise of blood sugar occurred with the small doses and when the rabbit showed no nervous symptoms. This conclusion is supported by the beneficial effects resulting from preceding injections of sodium bicarbonate. The results with glucose, although not so striking as those with bicarbonate, are of interest in that they are in accord with what has been long known clinically, viz. : that administration of glucose is one of the best methods of treating a ketosis.

At the same time it is very clear from our results that the effect of acetone is not limited merely to an alteration of the acid base balance. It has also a direct action on the central nervous system not unlike that of alcohol, particularly methyl alcohol, the toxic action of which is frequently manifested by convulsions. This narcotic action is apparently influenced by the presence of alkali and glucose, and in order to produce it large doses of acetone must be injected.

It would seem that this double action of acetone is frequently lost sight of in assessing the influence of various factors in the production of coma. As has been pointed out by many investigators[8] [17], it is hardly fair to compare the results of an acute intoxication with acetone on the cells of an animal that is previously normal, with the gradual and continuous action of small percentages of acetone over long periods. In the latter case the acetone is having a continuous effect on the acid-base equilibrium and the organism is in a condition of stress in the constant effort to maintain a normal reaction. It may be that in this way the cells become more liable to the narcotic action of acetone so that at a certain stage in the condition with the gradual rise in the acetonæmia, coma sets in, although the actual percentage of acetone is much below that found to be necessary for the experimental production of coma.

Conclusions.

1. Experiments were done on cats and rabbits to demonstrate the effects of acetone administered intravenously.

2. Doses of acetone exceeding 0·8 cc. per kilo body weight produced unconsciousness, occasionally with clonic convulsions. The respiratory minute volume was increased. The blood pressure was lowered, with a preliminary slight rise, on a few occasions.

3. In each case the urine was free of ketone bodies within twenty hours of the administration of acetone, irrespective of the dose.

4. In all cases but one there was a slight but definite rise in blood-sugar following intravenous injection of acetone.

5. In two cases the CO_2-dissociation curve of the arterial blood was determined, and the pH of the " arterial " point calculated. In both cases there was a slight shift to the acid side.

6. Previous or simultaneous injection of glucose or sodium bicarbonate always lessened the intensity of the acetone effect. Sodium bicarbonate seemed slightly the more efficacious.

7. The suggestion is made that acetone has a double action : (1) a toxic effect similar to that of methyl alcohol and (2) an acid effect on the acid-base equilibrium.

We desire to thank Professor L. Findlay for his helpful advice and criticism throughout the course of the research. Our thanks are also due to the Medical Research Council with whose aid the work has been done.

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A CLINICAL, PATHOLOGICAL AND BIOCHEMICAL STUDY OF AMYLOID NEPHROSIS.

BY

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The conception of a degenerative form of nephritis as opposed to the common inflammatory form, whether justified or not, has been the source of many valuable observations on the clinical, chemical and histological aspects of the subject. The term " nephrosis " was introduced by Müller[1] to indicate the purely degenerative form, and since the degeneration is frequently of the fatty type, the term " lipoid nephrosis " has been used by many writers on the subject. It appears, however, that there is no hard and fast line between ordinary glomerulonephritis and nephrosis, and that all combinations of glomerular and vascular inflammation with tubular degeneration may be found. Nevertheless it remains convenient to distinguish a group in which the signs of inflammation are conspicuously small.

In this group of cases it is found that there is a remarkable absence of cardiovascular abnormalities, such as raised blood pressure, cardiac hypertrophy, retinal hæmorrhages and exudates, hæmaturia and anæmia, but that there is an equally remarkable liability to œdema. The fact that complete recovery may occur even after years of obstinate œdema and proteinuria makes the recognition of this condition of more than academic interest from the aspect of prognosis. Biochemical studies show that there is unimpaired ability to excrete urea and that the blood urea is sometimes exceptionally low. The blood uric acid is slightly raised. Water and sodium are excreted with difficulty, and the balance of water and salts in the tissues is upset[2]. The albumin of the plasma is greatly reduced, more so than in glomerulonephritis with œdema, and the globulin is slightly increased[3]. The plasma is often milky in appearance and contains an excess of fatty acids and cholesterol.

In slight and temporary cases the pathological lesion is confined to cloudy swelling of the parenchyma of the kidney, but in graver cases it passes into a form of " large white (or yellow) kidney " in which quantities of simple and anisotropic fat appear in the epithelium of the tubules and later in the interstitial tissues. Occasionally the deposits of fat are so extensive that the condition is that described by McNee, under the name of " myelin kidney "[4]. The deposits of cholesterin provoke an inflammatory interstitial reaction and the denuded tubules disappear with degeneration of their glomeruli. The kidney as the result of these changes becomes small, and fibrous tissue develops in it. Ultimately a " nephrotic contracted kidney " is produced (Volhard and Fahr[5]), and this is associated with failure of renal function but not with

increase of blood pressure or its concomitants. The final stage is rarely seen, for most of the victims of this disease succumb to the perils of their waterlogged state or to an intercurrent infection.

Two other pathological states not uncommonly complicate the picture, namely, arteriosclerosis and amyloid disease. Amyloid disease of the kidney may occur apart from lipoid nephrosis and in that event its sole symptom is proteinuria. When it is associated with nephrosis the symptoms are those of uncomplicated nephrosis, from which therefore it cannot be recognised during life (Volhard and Fahr[5]).

The case reported here was diagnosed as one of "nephrotic contracted kidney" and the presence of amyloid, though suggested by the history, was unrecognised. Detailed studies of the clinical course and the chemistry, particularly of the inorganic radicles, of this late stage of the condition are scanty, and it is for this reason that the case is presented.

Case.

History. The patient was an undersized and deformed boy of 13 years. At the age of four he had mastoid operations performed on both ears; the left healed but the right continued to discharge from time to time. A few weeks after the operation his face became puffy and his legs œdematous. In the following years the swelling had come and gone and he had been in hospital for it more than once. In 1925 he was sent to St. Bartholomew's Hospital for treatment of his ear. On examination his neck was found to be rigid and his right knee full of fluid; for this latter and for his stunted growth he was referred to the orthopædic department where it was found that he had œdema and proteinuria.

He was admitted to a medical ward on October 29th, 1925. He complained of nothing except the swelling. His weight was 74 pounds. He had scabies. The face was pale and puffy but the mucous membranes were of good colour. The neck was rigidly fixed and no rotation of the head on the trunk was possible; he peeped out of the corners of his eyes. The optic discs were blurred but there were no hæmorrhages or exudates into the retina; the veins were engorged and the vessels tortuous. Both ear drums were perforated and from the right ear there was a copious discharge of pus; there was a small sinus over the right mastoid. Tonsils and pharynx were healthy. He was pigeon-chested with wide and prominent subcostal angle. It was difficult to estimate the size of the heart exactly, but the apex was in the fourth space 3 in. from the midline and the cardiac impulse was somewhat forcible. The heart sounds were not abnormal. The blood pressure registered 112/72 mm.; the arteries were not thickened. The lungs were normal. The abdomen was generally distended but without definite signs of free fluid. The liver, spleen and kidneys were not palpable. There was œdema of the whole body, especially of the face, legs and sacral region, and a painless effusion into the right knee joint. Blood examination: red cells 4,800,000, hæmoglobin 78 per cent., white cells 10,800, urea 27 mg. per 100 cc., Wasserman and Sigma tests, negative. Urine: S.G. 1,005 to 1,030, pale and clear, protein 0·3 to 0·8 per cent., no sugar; quantity 200 to 1,000 cc. a day. Urine deposit contained a few pus cells, an occasional red blood cell and a few granular casts. Urea feeding test (14.11.25): maximum concentration, 2·5 per cent. in the first hour; maximum output, 1·4 gm. in second hour.

Course and Treatment. The œdema decreased somewhat soon after admission but remained massive. Urea therapy (10 gm. a day) was given from November 16th to December 24th; it was quite ineffectual although the blood urea increased to 90 mg. A few days after it was discontinued, the blood urea had fallen again to 39 mg. On December 9th an operation was performed on the right mastoid, after which the discharge from the ear almost disappeared.

The knee became very tense and painful, and it was aspirated on several occasions; the fluid obtained was purulent, but it was sterile and its inoculation into a guinea pig did not result in tuberculosis. X-rays did not reveal any disease in the knee, and showed that the stiffness of the neck was due to fusion of the laminæ of the vertebræ.

On January 9th, 1926, traces of sugar appeared in the urine. Until this date daily examination of 24-hour specimens had failed to show any sugar, but from this time onwards it was always present in small but definite amount. A blood-sugar curve after 50 grams of dextrose showed a rise from a fasting figure of 0·9 per cent. to a maximum of 0·11 per cent. at the end of an hour; the sugar in the urine was not appreciably increased. A lowering of the threshold for sugar was therefore present, similar to the lowering of the threshold sometimes seen in the terminal stages of glomerulonephritis(6).

From December 28th a strict salt-free diet was given, the amount of fluid taken being limited as before to 1,200 cc. a day. The régime was very successful in reducing the œdema and in improving his general condition. He became free of œdema. On February 17th he was not so well, and on the following days he developed headache, vomiting, drowsiness and twitching of muscles. The breathing became slow and deep. A general erythematous rash appeared. The output

CHART I.

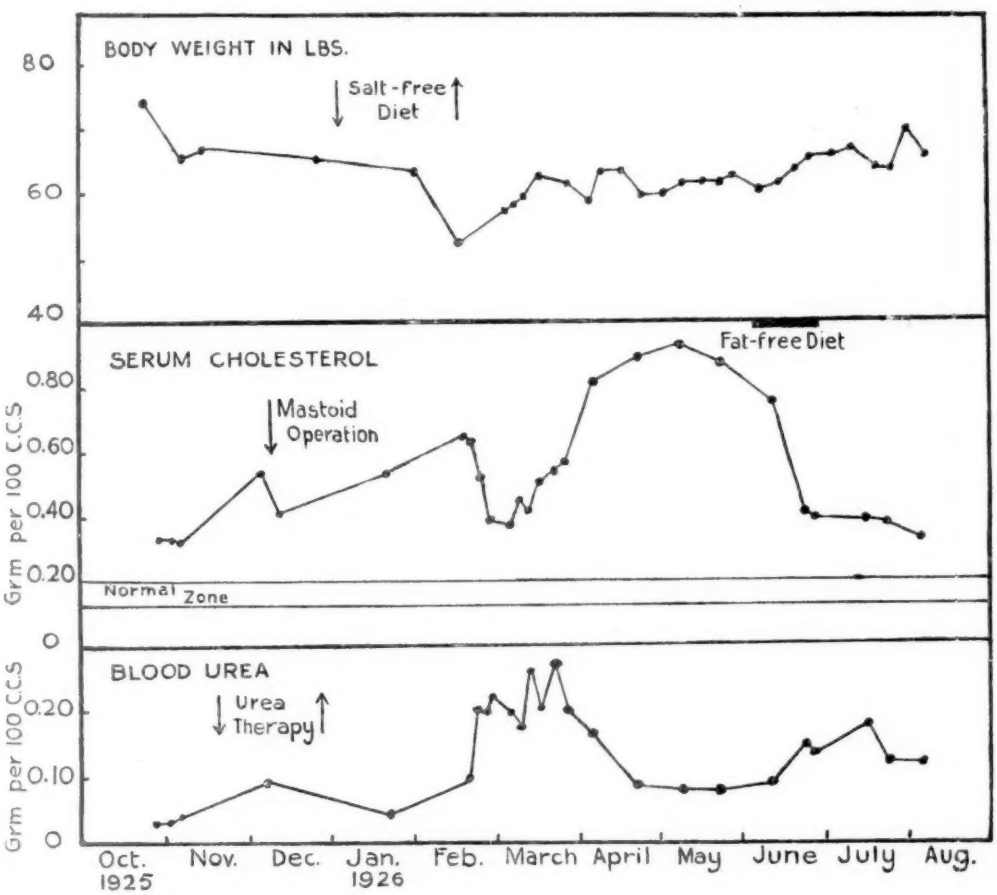

Chart I. The three curves indicate the variations in body weight, serum cholesterol and blood urea.

of urine was only 300 to 500 cc. a day, but he appeared desiccated, not œdematous, and his weight had fallen to 52 pounds. The blood urea which was 90 mg. on 18th, had risen to 199 mg. on 24th, and the serum gave Andrewes's diazo reaction of uræmia(7). He became rapidly worse and was thought to be dying. From the commencement of this change for the worse he was encouraged to take extra fluids, and on the 22nd this was supplemented by giving rectal salines. Food restrictions were relaxed.

CHART II.

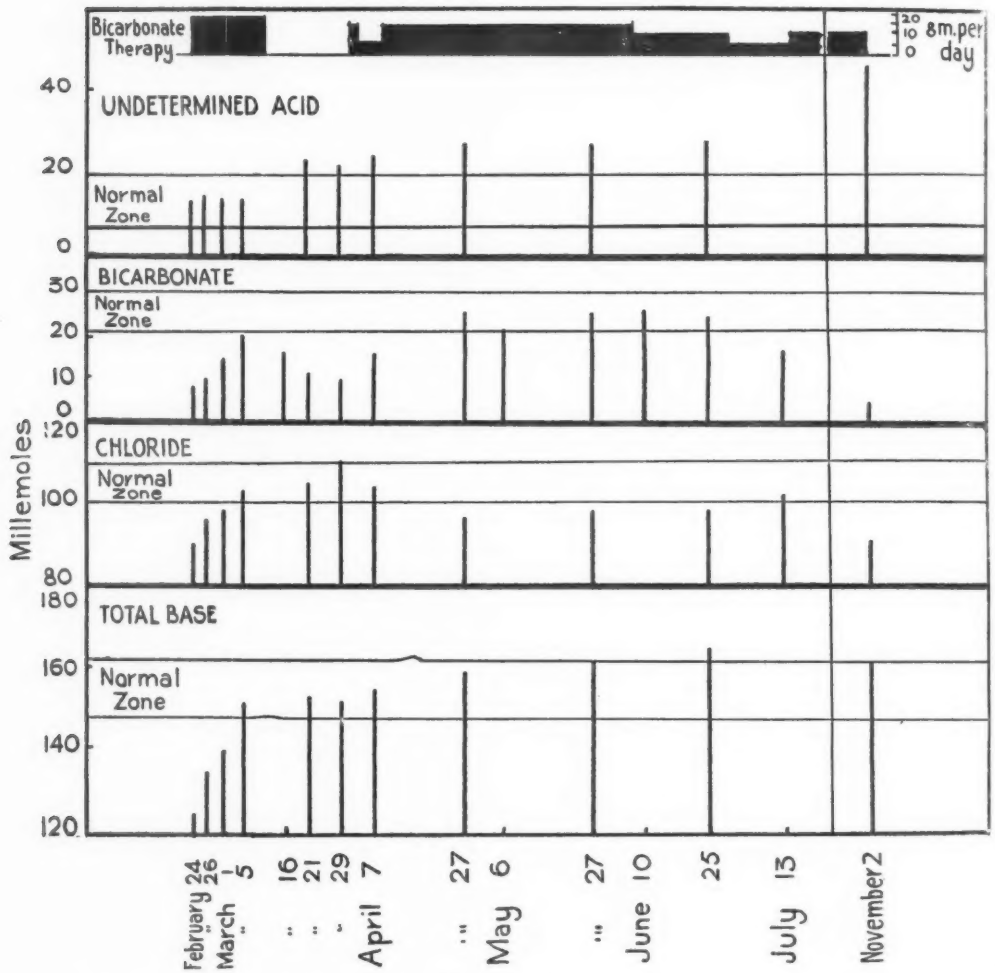

Chart II. The four series of columns indicate the concentrations of " undetermined acids." bicarbonate, chloride and total fixed base in the serum in millemoles per litre. The zone of normal variations is indicated by the two lightly drawn horizontal lines in each compartment of the chart. Bicarbonate therapy is shown by the solid figures in the uppermost compartment.

On February 24th a complete examination of the inorganic constituents of the serum revealed an extremely abnormal state. The CO_2 content had fallen to 14 volumes per cent. and the *p*H to 7·05, so that there was present a very extreme uncompensated acidosis (acidæmia). In addition to this there was a great reduction of the total inorganic bases and chlorides. The condition was interpreted as a combination of uræmic acidosis with a deficiency of base and chloride due to the prolonged salt-free diet. (Chart II and Table.)

TABLE I.

Variations in total acid-base balance in the serum of H.B.

Date.	Protein.	*p*H.	Base bound by				Total Base.	Base bound by	
			HCO_3	Cl.	PO_4	Protein		Determined Acids.	Undetermined Acids.
	gm. %		mM.	mM.	mM.	mM.	mM.	mM.	mM.
24/2/26		7·05	8·1	89·5	7·0	(7)	124	112	12
26/2/26			10	96·0	(7)	(7)	134	120	14
1/3/26		7·14	14·9	98	(7)	(6)	139	126	13
5/3/26	4·0		20	103.5	4·2	6	151	134	17
16/3/26			15		4·3				
21/3/26		7·17	11·5	105	(4)	(6)	152	126	26
29/3/26		7·16	8·7	110	(4)	(6)	151	129	22
7/4/26		7·20	15·9	104	(4)	(6)	154	130	24
27/4/26		7·41	26·0	96	(4)	(7)	159	133	26
6/5/26	3·8	7·33	21·5		3·5	6·5			
27/5/26	3·8	7·24	26·1	98	4·1	6·5	161	135	26
10/6/26			28						
25/6/26	4·7	7·24	24·4	99	4·0	7·8	164	135	29
13/7/26			17	101					
2/11/26		7·15	4·6	91	11·5	(7)	161	114	47

( ) Figures in brackets were not determined on the date given, but are approximated from the closest data. To obtain the figure for mm. of base bound by protein it was necessary to know both protein concentration and *p*H; it was then calculated from the formula $[BP_s] = 0{\cdot}068\ [P_s]\ (p\text{H} - 4{\cdot}80)$. (Van Slyke, Wu and McLean, *Journ. Biol. Chem.*, 1923, LVI, 765.)

Fluids were then forced upon him to the extent of 2,500 cc. a day, and 5 grams of sodium bicarbonate were given four times a day. The result was a striking relief of his symptoms, but in the course of a few days the œdema returned to a very great extent. The inorganic bases gradually increased in the serum but it was three weeks before the normal level was attained. Chloride increased in a similar way, but the CO_2 was still below normal at 48·7 vols. per cent. when it was thought desirable to stop giving the bicarbonate on account of the increasing œdema (March 8th). To counteract this the fluid intake was reduced to 1,200 cc. and the diet was moderately restricted generally and in respect to salt. At this time he was comfortable and happy, and his appetite was good although he still vomited occasionally. The blood urea remained in the region of 200 mg. The CO_2 content had fallen to 28 vols. by March 21st and an attempt to counter this fall was made by giving disodium phosphate. A moderate diuresis was the result, but the CO_2 content continued to fall.

On April 1st the phosphate was replaced by bicarbonate in doses of 15 grams a day. Two days later tetany was present. It was attributed to an alkalosis due to excess of bicarbonate, but unfortunately no blood examination was made. The tetany was quickly removed by a dose of 10 grams of ammonium chloride and the bicarbonate was reduced to 5 grams a day.

The vomiting had not been at all severe for some weeks and by this time had ceased. Four days later the serum-contained 38 vols. of CO_2 and its *p*H was 7·20, so that it appeared improbable that there had been an alkalosis severe enough to have been the cause of tetany. The serum calcium was low, 6·1 mg. per cent., but the significance of this low figure as possibly productive of the tetany is discounted by the fact that the serum protein was also very low, 3·8 per cent. Salvesen and Linder[8] found that the serum calcium in nephritis with œdema always fell with the protein without the development of tetany; under these conditions the serum calcium was found as low as 6·3 mg. It appeared possible that with this low concentration of calcium and protein the body might have become more sensitive to decrease of hydrogen ions, and that the tetany might have been evoked at the normal blood reaction. To gain information on this point, the bicarbonate was increased on 13th to 15 grams a day, but although the CO_2 increased to 61 vol. and the *p*H to 7.41, the tetany did not recur.

In June the daily dose of bicarbonate was reduced to 10 grams and then to 5 grams. The CO_2 began to fall after the second reduction, so the dose was again increased to 10 grams.

In May he was up and allowed out in the hospital square. The blood urea had fallen in April from 200 mg. to 80 mg. at which level it remained till June when it began to rise again. In July there was no œdema except some puffiness of the face. His basal metabolism was −23 per cent.

He went home on August 12th. Since admission the blood pressure had not increased and the heart had not enlarged. The urine still contained a large amount of protein but no red cells or casts. The hæmoglobin had fallen to 38 per cent. during his uræmic attack and was the same in August; the red cells numbered 1,850,000. The blood urea was 118 mg. The specific gravity of the urine varied only from 1,008 to 1,014.

He remained in the same condition, taking bicarbonate regularly, until the end of October when he caught an acute coryza. After two days of vomiting and diarrhœa he became much worse and was brought to hospital. He was then in a moribund state. There were signs of bronchopneumonia in both lungs. Dyspnœa was extreme. Neither liver nor spleen was palpable. There was no ascites, and no œdema was present except for moderate pitting over the shins. The CO_2 content of the serum had fallen to the very low figure of 11 volumes per cent. The pH was 7.15. The non-protein nitrogen was 187 mg. per cent.

He died 30 hours after admission. The clinical diagnosis was chronic nephritis (chronic nephrosis in final stage of contraction) bronchopneumonia.

Autopsy.

The body was poorly nourished. The face was puffy, but there was no other œdema.

Heart, 7 oz. Pericardium was obliterated by fine recent adhesions. No hypertrophy, slight dilatation. Valves, aorta and coronary arteries, healthy. *Pleuræ*. Right sac was obliterated by soft adhesions in the meshes of which was yellow pus. Left was similar, but there was a collection of 150 cc. of pus at the back of the lower lobe. *Lungs:* both contained areas of confluent bronchopneumonia. *Peritoneum:* healthy. *Liver:* rather large and pale with rounded edges. *Spleen:* 6 oz., somewhat enlarged and firm; on section it was bloodless and the Malpighian corpuscles were enlarged and translucent ("sago" spleen).

Kidneys. R. 2¾ oz., L. 2½ oz. Both kidneys were much reduced in size. The capsule stripped with a little difficulty being bound to the cortex by fine adhesions. The exposed surface was very finely granular and of a pale yellow colour. On section the pelvic fat was seen to be increased, but the pelvis was not dilated. The cortex was moderately decreased in width, in some parts extremely so; it was yellowish grey in colour and in it translucent specks could be seen representing the glomeruli. There appeared to be both fibrous and fatty changes. The pyramids were somewhat atrophied, but retained their normal colour and markings. The blood vessels were not abnormally apparent on the cut surface. *Bladder and ureters:* healthy.

Brain. No examination permitted.

The laminæ of the cervical vertebræ were fused, but the bodies of the vertebræ and the intervertebral discs were sound. The right thigh and calf were wasted, and the knee joint showed no changes except a small erosion of the articular cartilage.

The heart's blood contained pneumococci.

Histological Report.

The Kidneys. Sections were stained with methyl violet (for amyloid degeneration); hæmotoxylin and oesin; Van Gieson; hæmotoxylin and Sudan III (frozen sections prepared by Gaskell's gelatin technique[9]). Fresh sections also were examined under a polarising microscope.

As will be seen from the illustrations the sections of kidney presented a remarkable appearance. The most striking thing about them was the appearance of the glomeruli which, almost without exception, were enormously swollen and homogeneus. In size each appeared about twice the normal. Stained with hæmotoxylin and eosin they assumed a uniform pinkish tinge. With hæmotoxylin and Sudan III they remained unstained, except for certain areas of fatty degeneration in many of them, and for a few endothelial cells in each which seemed to have escaped the general destruction. With methyl violet they gave the characteristic pink colour of amyloid material.

The Bowman's capsules were distended in every instance, and in places a small amount of "crescent formation" was to be seen. The epithelium of the tubules showed varying stages of fatty degeneration and atrophy. In a few small zones some apparently normal tubules were present; in others the contracting interstitial tissue had given rise to a few minute cysts.

The interstitial tissues showed a moderately active infiltration with round cells and fibroblasts, but the Van Gieson preparations revealed relatively little formed fibrous tissue. The smallness of the kidneys appeared to be due rather to degeneration and atrophy than to extensive inflammatory fibrosis.

The arteries showed changes of three kinds:—(1) Deposits of amyloid material, staining pink with methyl violet and best seen in the tunica media of the smaller vessels; (2) intimal thickening and hyaline change in the interlobular arteries; (3) endothelial proliferation and fatty degeneration in the intima of the arterioles. Changes (2) and (3) were precisely similar to those occurring in older patients with diffuse hyperplastic arteriosclerosis and high blood pressure. Evans[10] has pointed out that it is not unusual to find these lesions *confined to the kidney* in many types of nephritis and that a diagnosis of diffuse hyperplastic sclerosis cannot be made unless they are present in other organs, notably the spleen. In this patient sections of the spleen, stained for fat, failed to show such lesions.

The appearances in the kidney, then, were those of a wide-spread degeneration and the inflammatory element was not marked. The nature of the degenerate material was amyloid with a fair amount of fat. Examination of fresh sections with a polarising microscope demonstrated a little doubly refracting material in the glomeruli and the tubules, but this was not present to such an extent as to justify the term "myelin kidney."

Sections from the liver and spleen showed the presence of amyloid deposits; the liver also showed fatty degeneration.

Discussion.

1. *General.*

From the definite history of œdema recurring repeatedly during the preceding nine years, it seemed certain that chronic renal disease had been present for that time, and the atrophied state of the kidneys supported the opinion that the duration of the process had been a lengthy one. Since the œdema occurred first in weeks following a mastoid operation and its recurrences were associated with persistent aural sepsis, it seems very probable that this sepsis was the origin of the disease and the cause of its progressive course,

The discovery of amyloid degeneration was to be expected in a condition secondary to prolonged septic absorption, and should have been more definitely anticipated during life. The unusual sterile suppuration in the knee joint was considered to be another secondary phenomenon, and it is noteworthy that the trouble in this joint subsided when the primary focus in the ear had been attended to.

In the combination of a well marked tendency to œdema with a complete absence of hypertension and cardiac hypertrophy the case complied with the requirements for the diagnosis of " nephrosis." It was therefore an example of that condition in the terminal stage which is so rarely seen. It is of interest that with the onset of urea retention and uræmia the blood pressure did not rise although there was no evidence of heart failure to hinder it from doing so. The renal insufficiency was accompanied by wasting and anæmia as in glomerulonephritis, and the derangement of acid-base balance was profound.

2. *Cholesterol* (Chart I.)

The concentration of the plasma cholesterol was followed by the method of Myers and Wardell[11]; this method gives maximum normal values of 0·20 per cent. On admission (Oct. 1925) the plasma contained 0·33 per cent. and by December this had increased to 0·55. From this time the cholesterol rose steadily, reaching a maximum of 0·92 in May 1926. This steady rise was interrupted twice; first by a fall to 0·40 following the mastoid operation, and secondly by an irregular depression occupying the seven weeks of uræmia and acidosis in February and March. With the fall of the blood urea the cholesterol rose rapidly and attained the level to which it would have reached if its former rate of increase had not been interrupted. After reaching its maximum the cholesterol remained fairly constant for three weeks; a fat-free diet was then given, and this was accompanied by a fall to 0·40 per cent. in the next three weeks. On returning to a normal diet, the cholesterol did not rise in the six weeks following. No determinations were made from then till the time of death when the cholesterol had risen to 0·60 per cent. in spite of the presence of a severe infection.

It is well established that in hydræmic nephritis the plasma cholesterol is increased, but the meaning of this occurrence remains obscure. As shown in the present case the increase is not always proportional to the degree of œdema; for example, the highest cholesterol figure was obtained when no œdema could be recognised. The depression of the cholesterol which accompanies the uræmic state was also shown, and the possibility arises that the excessive cholesterol may be capable of reduction by a fat-free diet such as was recommended by Epstein for the treatment of these œdematous patients[12].

3. *Total Acid-Base Equilibrium.*

In the studies of this patient's serum we have an excellent example of the changes which occur in the balance of acid and base during the terminal stage of nephritis.

FIG. 1. x 85.

Methyl violet for Amyloid.

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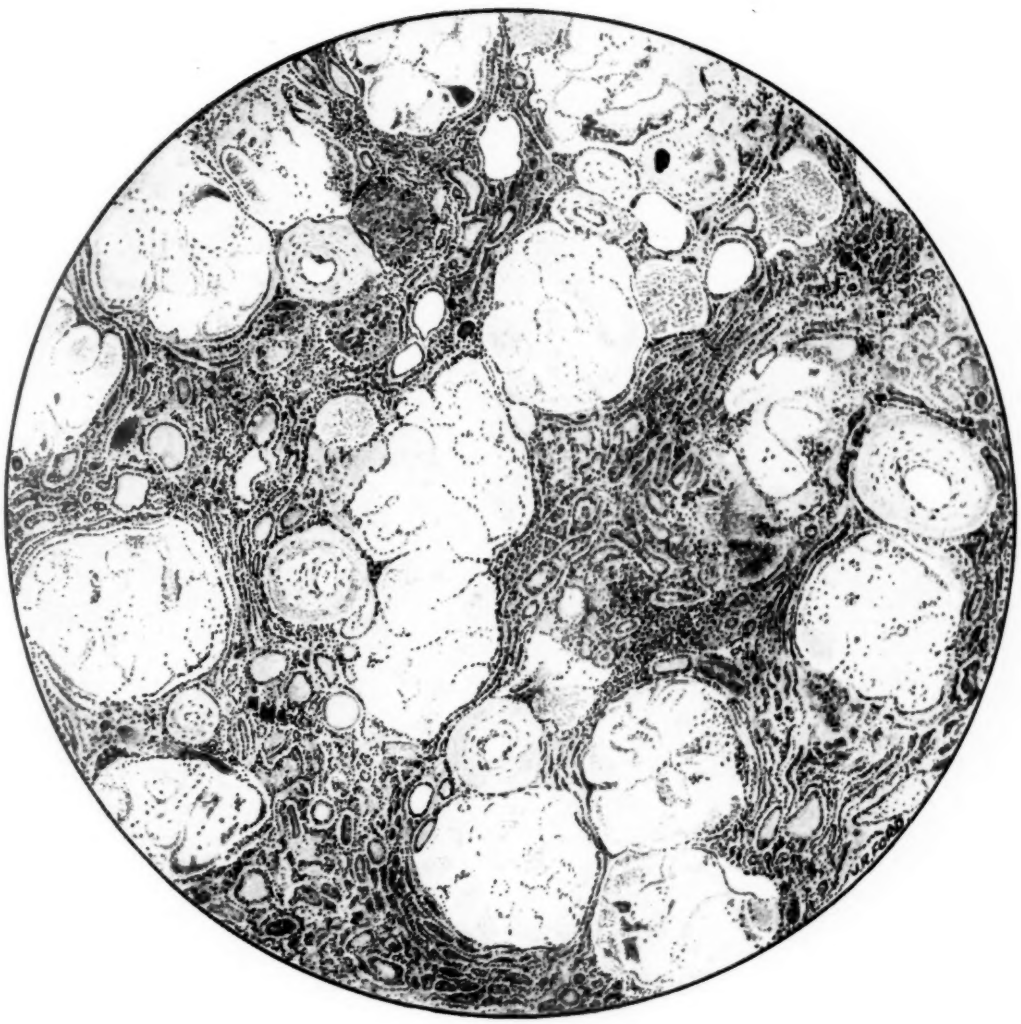

FIG. 2. x 85.

Sudan III and Hæmotoxylin.

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According to Peters[13] the average amount of base per litre of serum is equivalent to 156 millemoles of monovalent alkali. Of this an average of 103 millemoles are combined with chloride, 26 with bicarbonate, 3 with phosphate and 11 with the serum proteins which act as acids at the blood reaction. 13 millemoles remain unaccounted for, and since at the almost neutral reaction of the serum all the base must be combined with acid, it follows that there must be 13 mille-equivalents of acid substances in the serum over and above those already enumerated. These "undetermined" acids have not been identified but they comprise organic acids and a small amount of sulphate. The maximum concentration of these undetermined acids observed by Peters in his series of normals was 19·8 mM.

Bulger, Peters, Eisenman and Lee[14] showed that in the later stages of nephritis the undetermined acids were greatly increased. Their steady rise in the present case was of great significance. From Table I and Chart II it may be seen that, during the crisis through which the patient passed in February, these substances remained within the normal limits of concentration. But from the end of March they increased progressively in spite of improvement in the clinical state and of a falling blood urea. By June they had reached a titre of 29 mM. and just before death one of 47 mM.

Originally the term "alkali reserve" was applied to the base bound by bicarbonate, but it now appears that the base bound by chloride may become available for binding extraneous acids instead of, or as well as, that bound by bicarbonate. It will be seen from the chart that both these compartments of alkali reserve were encroached upon, once in February because of a deficiency of total base, and again in November because of the great excess of other acids, the concentration of base being normal. On the first of these occasions the condition was corrected by giving salt and sodium bicarbonate. When the latter was discontinued the serum bicarbonate at once fell and its place was taken by chloride and "undetermined" acid. When alkali was given again the bicarbonate rose and the chloride fell below normal The sum of chloride and bicarbonate tends to be more constant than either of its components.

In considering these changes in the alkali reserve of the serum it must not be forgotten that in whole blood between 70 and 80 per cent. of the total buffering power is due to the hæmoglobin which at blood *p*H acts as a weak acid. The base bound by hæmoglobin varies with the total hæmoglobin, its degree of saturation with oxygen, and the *p*H within the cells[15]. In the present case the great reduction in hæmoglobin in the later stages and the low *p*H indicated a great fall in this, the most important, reserve of alkali.

It seems very probable that the upset of February was precipitated by an unduly prolonged treatment with salt-free diet. Allen[16] has called attention to the occasional production of collapse in patients with hypertension who have been restricted to less than one gram of salt per day ; he maintained that no salt-free diet was effective unless such accidents did occasionally occur. The present instance is the first experience we have had of ill effects from this

treatment although numerous patients with œdema and a few with hypertension have taken for months diets on which the excretion of sodium chloride was less than a gram a day. In the present case the hypothesis of salt starvation would explain the desiccated appearance of the patient and also the chemical condition of extreme reduction of serum base (125 mM.) with corresponding fall in chloride and bicarbonate. The recovery of the patient coincident with their rise when salts were given lends a little further support to this opinion.

We attach little importance to the *p*H determinations because in some of the earlier observations it was impossible to obtain blood without stasis, although by means of hot arm baths this was avoided as much as possible. Fortunately on February 24th this difficulty did not occur.

The final figure for the CO_2 content is perhaps worthy of special comment ; 11 volumes per cent. is one of the lowest contents recorded in nephritis.

Summary.

1. This paper contains a clinical, histological and biochemical study of a case of " amyloid nephrosis " in its later stages.

2. The total acid-base equilibrium and the cholesterol in the serum were followed closely, and their clinical values are discussed.

3. The occurrence of tetany and of symptoms of salt deprivation are reported.

In conclusion we desire to express our thanks to Professor F. R. Fraser for the opportunity of studying this case, and to Dr. Geoffrey Evans for his kindness in lending us the reproductions of the sections of the kidney. One of us (G. C. L.) is also indebted to the Medical Research Council for a grant.

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ARTIFICIAL LIGHT THERAPY IN INFANCY.

A COMPARISON OF 66 CASES TREATED WITH THE MERCURY VAPOUR QUARTZ LAMP AND 137 CONTROL CASES.

BY

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Among the many varied and sometimes conflicting claims advanced for the beneficial effects of artificial light therapy, there appear to be only a limited number supported by objective evidence. Critics are now asking what proof exists of improvement in health arising out of the establishment of light clinics for children up and down the country, apart from those effects, such as the prevention of rickets, which may be obtained more simply by the use of cod liver oil. It seems, therefore, worth while to set forth the results of a controlled investigation of the effect of light therapy on infants under conditions similar to those existing at many light treatment clinics for young children.

The present investigation was undertaken in the hope of obtaining objective evidence of the value to the general health of city infants of the working classes of treatment with the mercury vapour quartz lamp ; evidence, for example, of better gain in weight, better hæmoglobin content of the blood, better resistance to infections, or better physical or mental progress.

Rickets and its associated respiratory infections, together with spasmophilia, were as far as possible eliminated from the control group as well as from the light-treatment group by the administration of cod liver oil during the winter. This was done for the reasons that the prophylactic and curative effect of ultra-violet light as regards rickets is fully established, and no further information on this question could be expected from the present investigation. It is obvious that for those effects which light and cod liver oil therapy have in common, cod liver oil (or possibly some other source of vitamin D), will be generally preferred as more economical in time and money. Moreover, the prevention of rickets by cod liver oil administration was indicated in the interests of the infants in the control group.

Statistical Presentation of Results (see Appendix). The whole of the statistical study of the weight curves has been carried out by Miss E. M. Newbolt, M.Sc., and other members of the staff of the Statistical Committee of the Medical Research Council who have also examined statistically the writer's findings concerning the effects of treatment upon the hæmoglobin percentage of the blood.

Clinical Material. All the cases in the series were out-patients attending the Queen's Hospital for Children or a light treatment centre in Bethnal Green, both situated in a poor and overcrowded district in the East End of London. The children belonged for the most part to working-class families. The economic status of out-patients of the Queen's Hospital is indicated by the following figures, very kindly supplied by the Almoner, Miss Grace Strangeways :—

Of 111 consecutive cases seen by her at the end of June, 1927, only 34 per cent. had a family income of over £3 a week, and 20 per cent. were in receipt of Poor Law relief or free milk grants, which may be taken as indicating that in these families the income was below a satisfactory subsistence level.

Of 276 cases in the series, 198 have records extending over periods of 1 to 13 months (13 months being the total period of the investigation). Of these, however, not all can be included in the comparison, as some received a small amount of light treatment such as rendered them ineligible for inclusion in either light treatment or control groups. The total considered here is 177 cases, but of these 26 are included for one period in the control group and for another period in the light treatment group, giving a total of 66 in the light treatment group and 137 in the control group. Of the controls a certain proportion attended irregularly, but the number eligible for inclusion in each set of comparisons is given under the different headings.

All children when first included in the series were under 18 months of age and were either entirely or largely fed artificially. When first seen, nearly all were under normal weight as judged, for example, by Griffith's standard weight curve for healthy breast fed infants (*see* Appendix). The majority were cases in which feeding had been unsuitable in quantity or quality ; a number attended with various minor complaints, such as constipation, intestinal disturbance, or slight bronchitis ; and a few were cases convalescent from some more severe illness, for example, pneumonia, or from an operation for pyloric stenosis. No cases of acute illness were included, but children developing such illnesses after inclusion were, so far as possible, followed up. Complete artificial feeding began at ages varying from one day to ten months, and 92 per cent. were entirely artificially-fed before six months of age. The type of artificial feeding advised was the same for both groups. It consisted in nearly all cases of dried milk, sugar and water, with orange juice, until the age of eight months, and thereafter mixed feeding. Cod liver oil was ordered for all cases during the winter. General advice as regards hygiene and management was the same for both groups.

From the purely scientific point of view the best contrast between " light " cases and controls would be obtained by minimising as much as possible outdoor life with its consequent exposure to sunlight. This was obviously not practicable in the interests of the children, and all mothers were urged to give the infants as much outdoor life as they possibly could, and it is probable that in consequence these children received rather more of it than the average among London children of this class.

Some of the infants in the series received iron. These cases are omitted when dealing with the effect of light therapy upon the hæmoglobin percentage of the blood, but are included in other sections of the work. Since they were distributed in both light group and control group this should not interfere with the validity of the findings.

Clinical Records. All mothers were asked to bring their babies for examination and advice at intervals varying from two to three days, (*e.g.*, during a period of food adjustment), to one, two or four weeks when the child was

progressing well. At each attendance the child was stripped, weighed and examined. All clinical notes were made by the writer, and included notes on the child's general condition and development, his colour, nutrition, appearance of health or otherwise, intercurrent illnesses, age of eruption of teeth and of standing, whether holding to a support or alone. Every child had the percentage of hæmoglobin in the blood estimated by Haldane's hæmoglobinometer, at, as far as possible, monthly intervals. Every estimation was made by the same observer, Miss Lorel Goodfellow, from blood drawn from a prick in the heel, precautions being taken to warm the foot if necessary.

Records of light treatment were entered from the Light Treatment day book on the child's weight chart by the Sister or nurse in charge.

Cases given Light Treatment. In the selection of cases for light treatment every effort was made to keep the two groups as evenly matched as possible. Comparison of the weights and of the ages of the children of the two groups at the outset shows that in these respects the groups were fairly evenly balanced (*see* Charts I and II and Tables E and C).*

One respect in which there was a great difference was in the frequency of attendance. The children in the light treatment group were asked to attend three times weekly (though only weighed and medically examined at longer intervals), those in the control group usually weekly, fortnightly or monthly, depending on such factors as the child's age and general progress and the length of the journey to hospital. Only mothers willing to go to much trouble for the sake of the child, and those not having a large family of young children, were willing to come up three days weekly, so that what advantage there might be as regards better maternal care probably lay with the " light " group.

As already mentioned, the advice concerning feeding and general management was the same for the children of the two groups.

Technique of Light Treatment. At the Queen's Hospital for Children (where all but 18 of the " light " cases were treated), the lamp used was a mercury vapour quartz lamp of the vacuum type, made by the Hewittic Company, on a direct supply current of 210 volts. All children treated at the Queen's Hospital had the skin sensitivity tested before light treatment was begun. Four small areas of skin on the abdomen were exposed for three, six, nine and twelve minutes, respectively, at one yard from the light, and the minimum erythema dose was recorded. The results for each month are shown in Table A. This table was compiled not from the infants of this series alone, but from children of ages up to 13 years. It will be seen that the average minimum erythema dose varied from 4·3 to 8·7 minutes exposure, and that approximately three-quarters of the cases showed erythema with three or six minutes' exposure. No doubt some cases would have shown ervthema with less than three minutes' exposure, but this was not tested.

Treatment was ordered three times weekly, beginning with a length of exposure just under the minimum erythema dose, but the exposure was divided, half to the anterior and half to the posterior surface, the child being entirely naked. For example, if reddening of the abdominal skin was obtained by six minutes' exposure, the child was given five minutes' total exposure, $2\frac{1}{2}$ minutes

* For Tables C.—G. and Charts I and II, *see* Appendix.

to the back and 2½ minutes to the front. The exposure was increased by 2½ minutes each time (1¼ minutes to each surface) to a total of 30 minutes, the aim being to avoid producing erythema. A few instances of reddening of the skin occurred, and, on a single occasion, after the fitting of a new burner, two or three cases were very slightly blistered.

At the light treatment clinic it did not prove practicable to determine the minimum erythema dose for each case. As the Hanovia lamp in use (vacuum type of mercury vapour quartz lamp, on alternating current of 240 volts.) was, at the beginning of the period, more powerful than the burner in use at the Queen's Hospital, the children were started with 2½ minutes exposure, increasing at alternate treatments by 2½ minutes to a maximum of 30 minutes.

The above-mentioned dosage, was, of course, entirely empirical, since dosage is at present unstandardised. Other workers use both more intensive and less intensive treatment.

TABLE A.

VARIATIONS IN THE MINIMUM ERYTHEMA DOSE IN 194 CASES TESTED AT THE QUEEN'S HOSPITAL (Mercury Vapour Quartz Lamp.)

Month.	*No. of Cases.*	*Smallest M.E.D.*	*Largest M.E.D.*	*Average M.E.D.*
1925.		Mins.	Mins.	Mins.
Oct.	29	3	12	8·0
Nov.	19	3	9	6·8
Dec.	25	3	12	7·4
1926.				
Jan.*	15	3	9	5·2
Feb.	14	3	6	4·3
March	18	3	9	5·3
April	16	3	12	6·0
May	15	3	6	5·8
June	11	3	12	6·8
July	12	3	9	5·5
August	5	3	12	8·2
Sept.	11	6	12	8·7
Oct.	4	3	12	6·7

* New burner, middle January.

Minimum Erythema Dose.	*No. of Cases.*	*Per cent. of total.*
3 Mins.	39	20%
6 ,,	102	53%
9 ,,	32	16%
12 ,,	21	11%

The Effect of Light Treatment upon Increase in Body Weight.

Rate of gain in weight is usually accepted as a useful criterion of an infant's state of health. It can never be the sole criterion, but in dealing with a group of infants under normal weight one might reasonably hope to see reflected in the weight curve any marked improvement, whether in general health or in resistance to infections. However, since happily the majority of such infants tend to improve in weight when obvious defects in their management are remedied, no deductions concerning the beneficial effects of one particular therapeutic agent are permissible without adequate control. Controls may be furnished either (1) by the rate of gain of the individual infants up to the time of getting the treatment in question (provided other factors in diet and management remain unchanged), or (2) by the rate of gain of a similar group of infants without this treatment. In infants the rate of gain tends to slacken fairly steadily with age, and moreover such factors as better adjustment of calorie needs might cause a rapid gain in weight after the first attendance, so that slight effects could easily be missed if the first method only were employed. A study of the form of weight curve in a limited number of cases revealed no obvious acceleration of growth from light therapy, and consequently the second form of control was the one selected.

The total number of cases in our series whose weights have been tabulated is 177 ; of these 26 have been included for some part of the time in the control group and for another period in the light treatment group, giving a total of 66 light treatment cases and 137 control cases.

There exists no satisfactory evidence whether the effect of light on the weight curve, if any, would be apparent within a few days or only after some weeks ; nor for how long it would be maintained ; nor on the amount of exposure necessary to produce an effect : consequently, some arbitrary standards had to be laid down before any comparison could be made.

(A) For the first comparison *all cases up to* 2 *years old and under observation for one month and upwards* were included, provided that *light treatment cases* (Group I) had had at least five exposures in every 28 days and a proportionate number for fractions of that time over 28 days ; and that *control cases* (Group II) had never failed to attend for a period of over 35 days. Many cases had more than one period of observation on this basis, *e.g.*, a child which lapsed, through failure to attend for six weeks, might subsequently be included for a second period. By setting the standard for inclusion somewhat low, cases having intercurrent illnesses, and therefore temporarily omitting their light treatment, or failing to attend on the day asked, were not excluded, and the total number of cases available for comparison was made as large as possible. It was hoped in this way to obtain an indication of improved growth from light treatment, even if only one in two or three of the children showed it, *e.g.*, only those getting less outdoor life than the average, or only those with a total dosage less or greater than the average.

There were 66 light cases, with 76 periods of observation, and 137 control cases, with 166 periods of observation. Table B shows that the periods under

observation averaged for light cases 14·6 to 16·2 weeks and for controls 13·7 to 13.8 weeks.

Light cases and controls were fairly evenly matched at the outset as regards the following factors :—distribution by age (*see* Charts I and II), sex (*see* Charts I and II and Table E), average age (*see* Table C), average deviation in lbs. from the normal weight (*see* Table G), average percentage deviation from normal weight (*see* Table E). It will be seen that both light cases and controls, when they first came under observation, averaged approximately 2·8 to 3·9 lbs., or about 18 to 23½ per cent. under normal weight (as judged by Griffith's standard weight curve for breast fed infants), that girls were lighter than boys, and that light cases were ¾ to 2¾ per cent. lighter than controls.

That the children both of the light group and the control group nearly all improved while under observation was obvious clinically, and is shown in the fact that they were, on the whole, nearer the normal weight for their age at the end of the period of observation than at the beginning (*see* Charts I and II). Light cases, however, did not have a definitely better average weight increase than controls. Table E shows this in figures : both light cases and controls were, on an average, about 6½ to 8½ per cent. nearer normal weight at the end of the period of observation, but among girls the light cases with lower initial weights showed approximately 2 per cent. more gain than the controls. The girl controls showed the same percentage gain as the boys of both the control and light groups. All these differences, including the 2 per cent. advantage over the controls of the light cases among the girls, are statistically " insignificant ;" that is, they are no greater than differences that might easily arise by chance (*see* Table F).

(B) For the second comparison only *light cases which had had more intensive treatment* (Group III), were selected, *i.e.*, cases with nine exposures or more per 28 days for six weeks or longer. By so doing, all children who had at the time any but the slightest intercurrent illnesses were excluded, as all such cases temporarily missed their light treatments. There were 39 cases with 57 periods of observation. All these cases were at the end of treatment under 18 months of age, and thus in this respect also had an advantage over the control group, since the rate of growth would normally be slower in the older children. Nevertheless, they show approximately the same increase in their percentage of normal weight as the whole control series : actually, it was very slightly less, but the difference amounts only to about ¼ per cent. to 1 per cent. of the normal weight and is, therefore, not significant (*see* Table E).

A *more strict control series* (Group IV) has also been taken for comparison, *i.e.*, cases which had not had any artificial light treatment at any previous date. Of these there were 115, with 137 periods of observation. As before, the gain, expressed as the average difference in the percentage of the normal weight at the beginning and at the end of the period of observation, is about the same, the controls having a slight advantage (*see* Tables E and F).

Certain advantages might have acted in favour of the light cases, *e.g.*, better maternal care, and, in the group with the more intensive treatment, the

automatic exclusion of cases with an intercurrent illness of any but the mildest type, together with the greater likelihood on account of the frequent attendances at hospital of early advice being obtained concerning any condition needing treatment. In spite of this, however, the average rate of gain in the light cases was almost exactly the same as in the control cases. This is true whether the group is taken as a whole, or whether only a more limited group receiving fairly intensive treatment over a period of six weeks and upwards is considered.

We may, therefore, conclude that the data obtained give no consistent evidence of any effect on weight, beneficial or adverse, produced by light treatment as here given to out-patient infants, (*see* Appendix by Miss Newbold below).

The Effect of Light Treatment upon the Incidence of Intercurrent Illnesses.

The treatment of young children in light clinics might influence the incidence of infectious illnesses either by improving the resistance to infection or by increasing the degree of exposure to infection.

In the cases under consideration, every effort was made to prevent the spread of infection from one case to another, but such a possibility cannot be set aside when young children are brought up by omnibuses and trams and collected into groups indoors. It is consequently possible that improved resistance might be masked by increased exposure to infection.

There was from week to week of the work no obvious difference in immunity between the two groups; coughs and colds were numerous in both, gastro-intestinal disturbances not uncommon, and neither were immune to the infectious fevers. A satisfactory statistical comparison of the amount of illness among light cases and controls cannot be made for reasons indicated later, but, for what it is worth, a statistical comparison was attempted. Winter and summer results are given separately, since there would be more likelihood of obtaining evidence of the beneficial effect of light treatment in winter when exposure to sunlight is at a minimum. Only illnesses causing a definite flattening in the weight curve or loss in weight were counted, with the exception of otorrhœa or the specific fevers, since, for the latter, weights were not available as the child did not attend for a varying length of time thereafter. Many criticisms can be brought against this attempt at comparison, *e.g.*, that cases having much intercurrent illness would drop out of the light group, that cases examined and weighed once weekly cannot fairly be considered with those examined and weighed monthly, and that a count of intercurrent illnesses is subjective and arbitrary. Nevertheless, bearing these facts in mind, the comparison seems worth making, if only to show that intercurrent illnesses were common in both these groups of sub-normal children. The light group included cases having five or more light treatments in each 28 days and attending for one month or more. No case was included in the control group which attended for less than one month, or failed to attend for over five weeks.

Table B shows the result of the comparison, but the writer would emphasise that whatever its value as a comparison, no significance can be attached to individual figures, owing to the subjective nature of such an estimate. Two points are worth noting :— (1) In winter the incidence of intercurrent illness is not unlike in the two groups ; (2) In summer the light cases show roughly double as many infections of the respiratory type, the figures otherwise showing no significant difference. The explanation of the different incidence of respiratory disease in summer is not clear, possibly it is the result of chance or of the difficulty of making a fair comparison. More probably, in the writer's view, it indicates the effects of greater exposure to infection among the light cases at a time of year when the control cases were spending the corresponding time out of doors.

TABLE B.
INTERCURRENT ILLNESSES.

	WINTER : OCTOBER—APRIL.				SUMMER : MAY—SEPTEMBER.			
	Non-Light Cases.		*Light Cases.*		*Non-Light Cases.*		*Light Cases.*	
Number of infants	70		48		78		32	
Total period in months for all infants ...	196		137¾		218¾		83½	
Average period of observation in months per infant	2·8		2·87		2·83		2·61	
	No. of attacks	*No. of attacks per 100 cases per month.*	*No. of attacks*	*No. of attacks per 100 cases per month.*	*No. of attacks*	*No. of attacks per 100 cases per month.*	*No. of attacks*	*No. of attacks per 100 cases per month.*
RESPIRATORY DISEASES, ETC.—								
Sore throat ...	4	2·0	4	2·9	3	1·4	4	4·8
Cold in head ...	11	5·6 } 19·8	8	5·7 } 25·3	5	2·3 } 8·7	7	8·4 } 19·2
Bronchitis ...	24	12·2	23	16·7	11	5·0	5	6·0
Pneumonia ...	1	0·5	1	0·7	—	0·0	—	—
Otorrhœa ...	5	2·5	2	1·4	2	0·9	2	2·4
GASTRO-INTESTINAL, ETC.								
Diarrhœa and vomiting ...	12	6·1	14	10·1	25	11·4	7	8·4
Stomatitis ...	4	2·0	—	—	2	0·9	1	1·2
SPECIFIC FEVERS.								
Measles ...	10	5·1	6	4·3	1	0·5	—	—
Diphtheria ...	—	—	1	0·7	—	—	—	—
Scarlet Fever ...	—	—	—	—	1	0·5	—	—
Whooping Cough	—	—	—	—	1	0·5	—	—
PYREXIA (? cause)	5	2·5	2	1·4	3	1·4	—	—
ABSCESS ...	1	0·5	—	—	1	0·5	1	1·2
ADENITIS ...	1	0·5	—	—	—	—	—	—

TABLE B.—Except in the case of the infectious fevers and otorrhœa, only illnesses known to have caused a loss in weight or definite flattening of the weight curve have been included in this table.

This comparison, therefore, gives no evidence that light treatment as here given increased resistance to infection.

The probable incidence of intercurrent illness in the light and control groups respectively, had cod liver oil medication been omitted throughout, is of interest, and some facts bearing on the point are available. The writer made a similar comparison some few years ago of the amount of illness in two groups of infants, one group getting cod liver oil, the other on a diet which failed to protect from rickets.[1]. The children were all artificially fed and were in-patients living in an institution in Vienna. The results showed that in winter (when the children were out of doors very little), respiratory diseases were much more common in the group unprotected from rickets; but that in summer (when the children were usually out all day and consequently rickets as diagnosed radiographically was prevented or cured), there was but little difference between the two groups. It may be taken as certain that rickets would have occurred in our present control group if these children had not been protected by cod liver oil, since among 169 new out-patients under two years old at the Queen's Hospital in April, 1924[2], 15 or 9 per cent. (8 per cent. if two cases sent up for rickets are excluded), showed radiographic evidence of rickets in spite of the fact that many of them had been protected by the administration of cod liver oil given at welfare centres. We may, therefore, presume that had the present control group, all artificially fed from an early age, received no specific anti-rachitic treatment, a considerable number would have shown a diminished resistance to respiratory infections as compared with the light group.

The Effect of Light Treatment upon the Hæmoglobin Content of the Blood.

The percentage of hæmoglobin in the blood of the infants in both groups, together with its variations and the data upon which the following statements are based, will be more fully considered in a separate paper, as results of considerable interest were obtained.

At present only the general results will be indicated :—(*a*) Individual cases of anæmia did not show an improved percentage of hæmoglobin in the blood as the result of light treatment.

(*b*) Light treatment, as here given, did not prevent the development of anæmia.

(*c*) No significant difference was found between the average hæmoglobin content of the blood in light cases and controls.

The figures obtained, therefore, show no evidence that light treatment with the mercury vapour quartz lamp, as here given, influenced in any way the percentage of hæmoglobin in the blood.

The Effect of Light Treatment upon the General Clinical Condition of the Children.

Any consideration of the effect of light treatment upon the general clinical condition of the children is necessarily upon much less certain ground than

the comparisons so far made, as it is for the most part based on entirely subjective impressions. Like most other clinicians who have used artificial light therapy, the writer's impression was that, at any rate during the winter, it was of benefit to a considerable proportion of hospital children in sub-normal health. Mothers frequently state that an infant, or toddler, having light therapy is happier, brighter, cries less, eats and sleeps better than before, though in a few cases wakefulness at night appears to follow too large a dose, even in the absence of any obvious skin effect. However, there is no doubt that nowadays suggestion plays a great part in the effects obtained by light therapy, and although to the mothers peaceful nights may be objective facts, the physician told of the improvement in sleep must rate the evidence as subjective.

The contrast, if any, between light cases and controls should be most apparent during the late winter and spring months. An attempt was made to compare the clinical appearance of children getting light treatment with that of the control cases in winter by means of the author's notes made on each child at the time. This comparison includes 31 control cases and 36 light cases.

Nutrition and Colour. Judging from the notes on nutrition and colour made at the beginning of treatment, those cases given light treatment were definitely inferior to the controls in health. Nearly twice as many were marked " nutrition poor," and one and a half times as many " colour poor " or " colour fair." Reference to Table E will show that the weights of the children of the whole control and light groups will bear this out to some extent. Light cases were $\frac{3}{4}$ per cent. to $2\frac{3}{4}$ per cent. lower in weight than controls. Moreover in October, November and December, light cases averaged 5 to 2 per cent. lower in hæmoglobin than the controls. This initial difference in the groups was not intentional, and the author had attributed it to the fact that mothers of children who looked in poor health were more willing to expend time and trouble in bringing them up for light treatment. In the late winter months, as judged by the notes on clinical condition, the nutrition of children in the two groups was approximately the same, but the children of the light group had on the whole a better colour. The clinical notes, therefore, suggest that light cases as compared with controls were in poorer condition to start with, but probably in rather better general condition towards the end of the winter.

Age of Standing. Since, however, these findings are subjective, an attempt was made to determine whether children given light treatment were able to stand at a younger age than controls, on the supposition that the age of standing was a good objective indication of mental and physical development combined. Here again, however, the selection of cases for comparison was not easy, and the effort to include only cases in which the comparison seemed fair resulted in very small, and consequently inconclusive numbers :—23 light and 35 control cases. However, at each of the stages chosen, *i.e.*, standing holding to an object, walking holding on, standing alone and walking alone, the light cases showed slight superiority, *e.g.*, only 9 out of 24 controls, compared with 8 out of 12 light cases, could stand holding by 12 months of age.

Age of Dentition. The age of cutting teeth was also considered, but as one or two months light treatment would scarcely make any material difference to the age of dentition, and the number of cases getting a long period of treatment at the requisite ages was insufficient for comparison, no figures are given. Cases of delayed dentition were, however, found in both groups.

Speaking generally, it may be said that the subjective evidence furnished by the mothers' statements and by the writer's clinical notes of the children's appearance, suggests that light therapy did benefit the children's health to some extent.

Discussion.

Artificial light therapy may be regarded in two ways : either as an attempt to make good a defective exposure to sunlight, or as producing effects other than those of an optimum exposure to sunlight. The treatment of rickets is an example of the first, the treatment of neuritis by local blistering with light is an example of the second.

Generally speaking, the idea underlying the use of artificial light therapy appears to be that of making good the body's need of light. If this be so, two chief questions confront us : (1) what are the results of inadequate exposure to light ? ; and (2) does a large proportion of our population suffer from these effects ?

Our knowledge on the first point is at present very scanty. If we confine ourselves to infants, it may be said that two inter-related diseases are known to be directly associated with want of light, namely, rickets and spasmophilia. Judging from observations on infants living entirely indoors, and by analogy with experiments on animals living in darkness, both diseases could very probably be almost prevented in children living in total darkness by the administration of the anti-rachitic vitamin by mouth. Many hold that, excluding rickets and its associated respiratory infections, the defective health (*e.g.*, lassitude, poor appetite, increased liability to infections), found in children living an indoor life in institutions, is partly due to inadequate ultra-violet light, but this view does not appear to be satisfactorily proved.

Concerning the second point, the prevalence of rickets in our cities among children unprotected by cod liver oil affords ample proof that a great many children suffer from inadequate light in the winter. Since, however, active rickets is rare in London by the early autumn, the existence in summer of widespread ill-health due to want of light only (as distinct from outdoor life) in this city is, in the writer's opinion, unproven.

In order to demonstrate the beneficial effect of light therapy, it is presumably necessary to treat children who have less than the optimum exposure to sunlight. There is little doubt that the control cases here studied fulfil that condition during the winter, since many similar cases have been shown to develop rickets at that season when unprotected by cod liver oil. In spite of this, however, a study of the weight charts, intercurrent illnesses and the percentage of hæmoglobin in the blood, supplies no objective evidence of the beneficial effect of light therapy in winter on children having cod liver oil.

Obviously a negative result such as this does not show that light treatment is without beneficial effect in such cases; in fact the writer's notes suggest that light therapy did to some extent improve the children's health, although such improvement was not demonstrated objectively by any of the three methods here employed. Objective evidence of the value of artificial light therapy might possibly have been obtained had the exposure to sunlight been less for all cases, or by the use of a different combination of rays from another source of artificial light, or by different dosage, but as regards this no information can be offered.

No attempt will here be made to deal with the large literature on the subject of light therapy in childhood, but it is of interest to compare results obtained by two groups of observers who have carried out somewhat similar investigations, remembering that specific diseases such as rickets, tetany, tuberculosis, asthma, hay fever, or diseases of the skin are not here under consideration.

Barenberg, Friedman and Green [3] carried out an investigation similar to that here described, but on in-patient infants instead of on out-patients. Twenty-one cases were treated with the mercury vapour quartz lamp, with 19 controls. All were given cod liver oil. They found as a result of light treatment no diminution in respiratory infections, no increased resistance to an outbreak of pertussis or of varicella, no evidence of hæmoglobin increase. They consider that there is evidence of an initial stimulation to increase in weight, but as this appears to be chiefly based upon the average absolute gain in weight of a light group with a mean age of 6½ months, compared with a control group with a mean age of 11 months, the opinion cannot be considered as substantiated. As regards muscle tone, however, the authors considered the children given light treatment as markedly superior. Their results, therefore, are very similar to those described in this article.

Pugh[4] at St. Mary's Hospital, Carshalton, where open air treatment is so extensively practised, has also studied the effect of artificial light treatment on the children's power of resistance to infection. He found no evidence of increased resistance (*e.g.*, to epidemic catarrh or chicken pox) among children given artificial light treatment. It seems possible, however, that his patients were already receiving optimum exposure to the light of the sun.

Summary.

Observations extending over thirteen months were made on the effects of treatment with the mercury vapour quartz lamp on the health of infants. The infants were out-patients, were artificially fed, came for the most part from poor and overcrowded districts in the East End of London, and were sub-normal in general health and in weight when they came under observation. The series treated with light numbered 66, the controls 137. All were given cod liver oil during the winter with a view to eliminating rickets and spasmophilia as a complicating factor from the investigation.

Weight. The rate of gain in weight of the controls was approximately equal to that of the light cases, whether the light group is considered as a whole, or comparison is made only with a section of cases having more intensive

treatment. What differences there are, are under 2 per cent. of the normal weight (Griffith's standard weight curve), and are probably due to chance.

Hæmoglobin percentage in the blood. This was approximately the same in the control and the light group. Light treatment did not cure or prevent the development of anæmia. The figures will be dealt with fully elsewhere.

Resistance to infection. A satisfactory comparison is difficult, but the amount of intercurrent illness in the light group and controls appeared to be about the same in winter. In summer the figures suggest that the controls showed fewer respiratory infections.

General clinical condition. The author's notes made at the time suggest that in the late winter and spring months, the light cases, as judged by colour, general nutrition and appearance of health, *seemed* to have made greater progress than the controls. Nevertheless, no objective evidence was obtained to support this.

It should be remembered that the negative results obtained from this investigation cannot be interpreted as necessarily in opposition to any positive findings obtained by others with similar cases ; since the dosage of artificial light is entirely empirical, different results might have been obtained with another type of lamp, *e.g.*, the carbon arc, and had the exposure to daylight been less for all cases, the contrast in light exposure between the two groups would have been greater.

The results have no bearing on the effects of light treatment on specific diseases which were not here under consideration.

The fact, that no objective evidence was obtained that light treatment as here given was of benefit to the health of the infants under consideration, emphasises the need of more investigation before authoritative statements can be made on the uses and limitations of artificial light therapy.

This work was made possible by the British Medical Association, who granted the writer the Ernest Hart Scholarship for the year 1925-26, followed by a second scholarship for the subsequent year, and to them my most grateful thanks are due.

I am greatly indebted to many persons for their generous help. Particular thanks are due to Miss E. M. Newbold, for her kindness in examining our data and reporting upon them. Miss Lorel Goodfellow has not only carried out all the hæmoglobin estimations, but has shared in every stage of the work. Sister M. W. Westbrook, who was in charge of the whole of the light treatment at the Queen's Hospital undertook the exacting work of keeping charts, and was ably seconded by the nurses. At the Bethnal Green Light Clinic, the assistance of Miss G. I. Le Geyt and the health visitors proved most valuable. To all these my gratitude and most sincere thanks are due.

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APPENDIX.

STATISTICAL EXAMINATION OF THE WEIGHT CURVES.

BY

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The National Institute for Medical Research.

An attempt is here made to examine statistically the question whether light treatment improves or does not improve weight. Whether or not weight is always a good criterion of improved health is a question outside our province, but even apart from this it is not easy on these data to give a definite answer to the simple question of increase or not. It is complicated by the fact that treatment began and ended with different babies at different ages over the first two years of life, when the weight changes rather rapidly, and also that the length of treatment varies, and the possibility exists that while light treatment might at first increase weight, prolonged treatment might have no further or even an unfavourable effect, so that by the end of long treatment the first increase might have been lost. It has also been found that with older children growth in weight varies with the time of year*, and the same may be true for babies, but I do not know of any data on this point.

On these comparatively small numbers sub-division by all these three variables is hardly practicable, and as *age* is probably the most important of them, we have confined ourselves to making some allowance for that.

The method adopted was to take a standard weight curve for these ages, find the deviations from the weight expected by this standard at the beginning and end of treatment separately for each baby and compare the *difference* between the deviations at the end and the deviations at the beginning, for the light and non-light groups. This has been done both for relative and absolute deviations. For the relative deviations we took the actual deviations expressed as percentages of the appropriate standard weight. The relative deviation seems the better measure to use, the only point of taking the absolute as well was the fear that the relative might be unduly influenced by the choice of standard. We have not been able to find a really appropriate standard for these data. We have used Griffith's Weight Chart (from the *New York Medical Journal*, 1899, LXIX, 295). This is a composite curve (male and female together) of healthy breast-fed babies of apparently different social classes and different nationalities, and it was chosen because it covers the whole range of the first two years of life. It is clearly much too high a standard for these babies, and might lead to very misleading conclusions if any one group—say the light group—were considered alone. As in our case we are only concerned with the difference between the light and non-light groups, of the excess deviation at the end of the treatment over that at the beginning, I do not think a fallacy is introduced as the light and non-light cases are scattered fairly equally over different ranges of age.

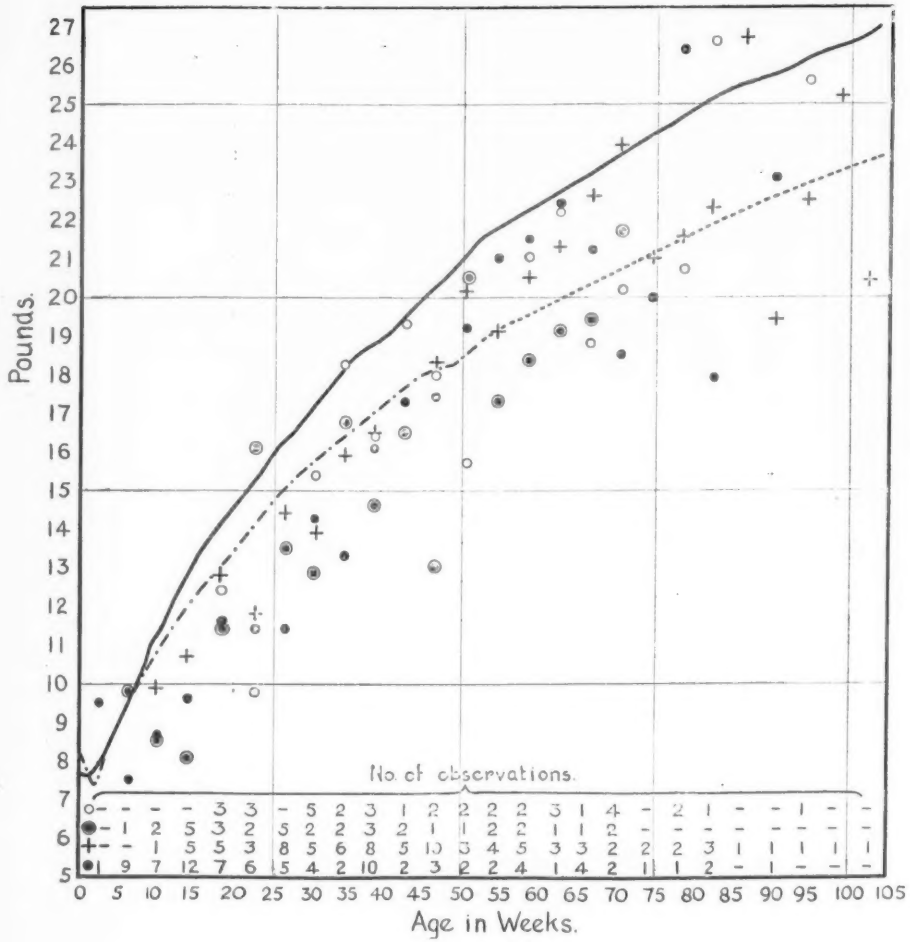
It would have been preferable to use a standard more appropriate to the data (the numbers are not large enough to make their own standard of the total), but I have not succeeded in finding one. The charts given (males and females separately) by K. Pearson and M. N. Karn*

* Dr. Corry Mann found both height and weight growth were more rapid in summer (1st April to 1st October) than winter in boys aged about 6—13 (Med. Res. Council, Spec. Rep. Series, No. 105). Dr. W. Camerer found his results with boys agreed with those of Malling and Hansen, for weight according to him the *maximum period* was August to mid-December, *middle period* December to end of April, *minimum* period end of April to end of July. In the latter period the loss of weight balances the increase in the middle period. The increase in the maximum period is three times as great as in the middle period. Height took a different course. Jahrbuch der Kinderheilkunde, Neue Folge 36-37, 1893-4, p. 975.

* "Study of the Data provided by a Baby Clinic in a large Manufacturing Town." Drapers' Company Research Memoirs. Studies in National Deterioration, X. Camb. Univ. Press 1922.

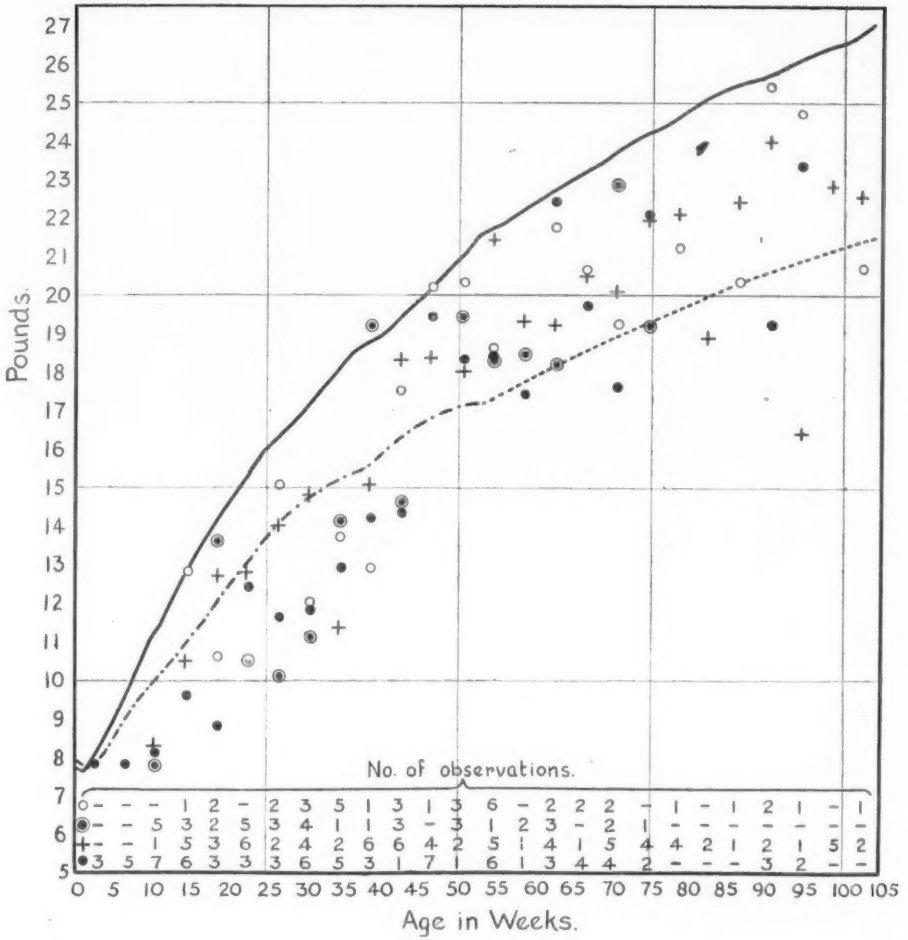
MEAN WEIGHTS OF INFANTS AT THE BEGINNING AND END OF THE PERIODS OF OBSERVATIONS.

MALES.



● Mean of Control cases, beginning of observation.
+ Mean of Control cases, end of observation.
⊙ Mean of Light cases, beginning of observation.
○ Mean of Light cases, end of observation.

FEMALES.



——— Griffith's Standard Weight Curve.
– – – – Pearson and Karn's Mean Weight Curve, first year.
..... Arbitary extrapolation from Pearson and Karn's first year values.

from a baby clinic in the north of England, are better suited to the data, but even they are too high, and also they only cover the first year of life. We tried producing them over the second year by reducing the Griffith second year weights in the same proportion that the Pearson-Karn weight at twelve months bore to the Griffiths weight at twelve months (see Charts I and II), but this seems rather arbitrary. The graph for females illustrates well the different conclusions that might be reached with the two standards, if the deviations in the first year of life were compared with those in the second for any one group.

Results.—Table E shews for males and females separately the relative deviations at the beginning and end of treatment for the different light and non-light groups. This table shews that the end relative deviation is always less in absolute value than the relative deviation at the beginning, but as has been pointed out before, this difference can only be interpreted with reference to the particular standard chosen. The differences with which we are concerned are given in Table F, which compares the light with the non-light groups. If *all* light cases (Group I) are compared with *all* non-light cases (Group II) the light show a small advantage in the case of females, too small, however, to be of any significance compared to the sampling error and in the case of males there is no difference between the two groups. In the selected light (Group III) and selected non-light (Group IV) for both females and males, the advantage is with the non-light groups, but here again the difference is too small to be of any weight compared with the error of sampling. Tables G and H give the same comparisons for *absolute* instead of relative deviations. In this case a very slight advantage is shown in all groups by the light cases, but the difference is smaller than its standard error and is also only between 1 and 3 ozs., so that no importance can be attached to it. If we make quite a crude comparison and do without a standard altogether, we note that the mean ages of the light and non-light babies at the beginning and end of treatment are as given below :—

TABLE C.

Mean Age in Weeks.

	Males.		Females.	
	Beginning of treatment.	End of treatment.	Beginning of treatment.	End of treatment.
Light cases ..	34·0 weeks	48·6 weeks	35·4 weeks	51·6 weeks
Non-light cases ..	32·0 „	45·7 „	39·1 „	52·9 „

so that the mean length of treatment is roughly the same for light and non-light babies. The graphs show also that the beginning of treatment is scattered over the age range about equally for light and non-light cases. It is, therefore, not so very unjustifiable simply to compare for the light and non-light groups the mean of each child's weight at the end of treatment expressed as a percentage of his weight at the beginning of treatment. The results of this show that by this comparison what small advantage there is lies with the non-light group in the case of males and with the light group in the case of females. The more exact method given above, using a standard curve, is, however, to be preferred.

TABLE D.

Observed Weight at End of Treatment expressed as a Percentage of the Weight at the Beginning of Treatment.

	Males.	Females.
Light cases	130·7%	137·7%
Non-light cases	136·5%	133·4%

All that we can say is that on the whole, these figures do not show any definite advantage in weight at the end of treatment of the light cases over the non-light cases. I think that it would not be justifiable to draw any general conclusions as to the effect of light treatment on the weight of babies in general.

TABLE E.

RELATIVE WEIGHTS AT THE BEGINNING AND END OF THE PERIODS OF OBSERVATION.

	Number of		At the beginning of the periods of observation.		At the end of the periods of observation.		Difference between the percentage deviation at the end and beginning of treatment. (B—A=X).	
Females	Obser.	Babies	Average % deviation (A)	Standard deviation.	Average % deviation. (B)	Standard deviation.	X	Standard deviation.
Group I	39	35	—23·47	14·23	—14·94	12·36	8·53	9·96
„ II	78	64	—20·70	17·00	—14·07	14·81	6·62	10·73
„ III	30	20	—17·30	13·50	—10·96	11·27	6·35	5·74
„ IV	63	54	—21·69	18·05	—14·69	16·16	7·00	11·17
Males								
Group I	37	31	—18·65	13·83	—12·11	13·42	6·54	6·35
„ II	88	73	—17·90	15·36	—11·52	13·77	6·53	9·78
„ III	27	19	—17·78	12·91	—12·33	11·41	5·45	4·27
„ IV	74	61	—18·92	15·31	—11·81	14·22	7·28	10·27

TABLE E. Shows in columns (A) and (B) the average percentage deviation from normal weight, i.e., the average for each group of cases of

$$\frac{(\text{observed weight}-\text{normal weight})\ 100}{\text{normal weight.}}$$

The standard of normal weight used was the weight for the age as shown in Griffith's weight curve. The mean percentage deviation, or the mean percentage above or below normal weight, is shown for each group of cases at the beginning and end of the periods of observation.

Group I. *Light cases* up to 2 years old, under observation for one month and upward, who had 5 or more exposures in every 28 days.

Group II. *Controls* up to 2 years old, under observation for one month and upwards, who never failed to attend for a period of over 35 days.

Group III. *Selected Light Cases* from Group I, up to 18 months old, under observation for 6 weeks and upwards, who had 9 or more exposures in every 28 days.

Group IV. *Selected Control Cases* from Group II who had had no previous period of light treatment.

NOTE.—The number of babies is less than the number of observations because some babies had more than one period of observation.

TABLE F.

DIFFERENCE BETWEEN THE PERCENTAGE INCREASE IN WEIGHT OF LIGHT CASES AND CONTROLS.

Difference between the mean % increase in weight of:	X of Light Cases *minus* X of Controls.	Standard deviation of Difference.
Females.		
Group I and Group II	1·91	2·00
Group III and Group IV	—0·65	1·75
Males.		
Group I and Group II	0·01	1·48
Group III and Group IV	—1·83	1·45

TABLE F. Derived from Table E. X= Mean relative deviation at end of period observation minus mean relative deviation at beginning of period of observation. (B—A=X).

TABLE G.

WEIGHT (IN LBS.) AT THE BEGINNING AND END OF THE PERIODS OF OBSERVATION.

	Number of		At the beginning of the periods of observation.		At the end of the periods of observation.		Difference between the deviation in lbs. at the end and beginning of observation. (D—C=Y).	
Females	Observ.	Babies	Av. dev. in lbs. (C).	Standard deviation.	Av. dev. in lbs. (D).	Standard deviation.	Y	Standard deviation.
Group I	39	35	—3·89	2·23	—2·96	2·30	0·92	1·56
„ II	78	64	—3·54	3·01	—2·82	2·91	0·71	1·60
„ III	30	20	—2·88	2·13	—2·07	2·01	0·81	0·92
„ IV	63	54	—3·57	3·24	—2·86	3·17	0·71	1·66
Males.								
Group I	37	31	—3·11	2·10	—2.32	2·47	0·79	1·11
„ II	88	73	—2·77	2·56	—2·17	2·62	0·60	1·59
„ III	27	19	—2·97	1·78	—2·31	1·91	0·66	0·71
„ IV	74	61	—2·83	2·54	—2·18	2·71	0·65	1·68

TABLE G. Shows the deviation in lbs. from normal weight. The standard of normal weight used was that shown in Griffith's weight curve.

TABLE H.

DIFFERENCE BETWEEN THE WEIGHT INCREASE IN LBS. OF LIGHT CASES AND CONTROLS.

Difference between the average increase in weight in	Y of Light Cases *minus* Y of Controls.	Standard deviation of difference.
Females.		
Group I and Group II	0·21 lbs.	0·31
Group III and Group IV	0·10 lbs.	0·27
Males.		
Group I and Group II	0·19 lbs.	0·25
Group III and Group IV	0.01 lbs.	0·24

TABLE H. Derived from Table G. Y= Mean deviation in lbs. at end of period of observation minus mean deviation in lbs. at beginning of period of observation=D—C.

SCIENCE AND THE BRITISH MEDICAL ASSOCIATION.

The B.M.A. report on rheumatic heart disease in children, published on July 3rd, 1926, is already bearing very practical fruit. Prior to the report the Manchester Board of Guardians had formulated a scheme of treatment of rheumatic carditis for the children under their care. These were admitted first to Booth Hall Infirmary for diagnosis and treatment until such time as they were able to have occasional exercise. They were then transferred to a private venture home for further treatment and regulated exercise, returning to Booth Hall if they relapsed and going home when sufficiently improved. On the publication of the report, the Guardians improved this scheme by providing " carditis " beds at their Children's Convalescent Home at Northenden, just outside Manchester. The complete scheme now consists of initial treatment at Booth Hall Infirmary until they are having one hour's exercise daily. They are then transferred to the " carditis " beds for regulated exercises until they can be transferred to the " convalescent " beds at the same institution. After a period of being up all day attending school to prove that the improvement is not evanescent, they are transferred home, but the Invalid Children's Aid Association will be asked for a monthly report. If relapse takes place during any of these stages, the child returns to Booth Hall and the procedure commences again. Authority has also been obtained for the services of a visiting cardiologist. This scheme therefore appears to provide Manchester children with everything that can be desired in the form of treatment and supervision when suffering from carditis.

The Metropolitan Asylums' Board are also moving in the matter very definitely, arrangements being made for the provision of 350 beds for cardiac cases at the Children's Hospital, Carshalton.

It is very gratifying to find that the action of the British Medical Association has so strengthened the hands of Medical Superintendents as to enable them to approach their Committees with a scheme which cannot be treated by a Committee, which must of necessity consider economy, as being merely a fad, even if a very laudable fad, of a public official. Probably other public bodies have already schemes under consideration.

ON DILATATION OF THE BLADDER AND URETERS IN CHILDHOOD

BY

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The purpose of this communication is to consider some of the conditions which may give rise during childhood to dilatation and hypertrophy of the bladder and ureters. Many instances of this nature have been already described and in some of these there has been an obviously demonstrable cause in the nature of some form of severe obstruction in the urinary tract: but in others post-mortem examination has revealed no organic obstruction, and for such various theoretical explanations have been suggested. These relatively rare conditions have recently been brought to our notice by the investigations carried out on five children under our care in the Hospital for Sick Children, Great Ormond Street, who presented symptoms either of intractable enuresis or of chronic infection of the urinary tract. In addition the opportunity has arisen of examining three cases post mortem: a study of these forms the basis of this paper.

Case 1. W. B., a boy, aged 6 years, was admitted to hospital, December 1922, with a history of enuresis since birth. It was at once apparent that the condition was unusual for there was enuresis by day as well as by night, and yet the bladder was so distended as to reach the level of the umbilicus. No obstruction was offered to the passage of a catheter although the condition was clearly one of retention of urine with overflow incontinence.

This boy suffered from great thirst and had frequent headaches. The urine was alkaline, with an S.G. of 1006, and pus and a cloud of albumen were present; sugar and ketone bodies were absent. The right kidney was easily felt. The blood urea was 114 mgm. per 100 c.c. (Dr. Harrison); systolic blood pressure 135 mm. Electrical treatment was tried, and this with urinary antiseptics improved the condition to some extent, and he left hospital but only to return later with a recurrence. Uræmic symptoms were now more obvious and steps were taken by Mr. O. Addison to obtain a more accurate diagnosis by pyelography. This showed a greatly dilated bladder and a tortuous left ureter with considerable distension of the renal pelvis. Shortly after this examination the boy died in uræmic coma. Unfortunately a post-mortem examination was refused.

It was this case which first drew our attention to the combination of painless enuresis with a distended bladder. In the light of later cases, it is very probable that had the boy lived long enough for a pyelogram of the right side to be taken, this ureter would also have been shown to be dilated.

The radiogram by Dr. Bertram Shires shows the condition that was present in the last period of the boy's life (Fig. 1).

CASE 2. T. G., a girl, aged 10 years, was admitted to hospital, April 1923, for abdominal pain and vomiting. There was a history of scarlet fever at two years of age. The patient was a well nourished child, the heart was normal, systolic blood pressure 100 mm. There was no fever, and neither kidney was palpable; the bladder was full and the urine always contained pus and albumen; S.G. 1010; on culture bacillus coli was isolated. Wassermann reaction negative. Blood urea 45 mgm. per 100 c.c.

The urea concentration test showed:—

Before urea	6 a.m.	1.45%
After urea	7 a.m.	1.18%
	8 a.m.	1.40%
	9 a.m.	1.45%

Mr. O. Addison examined with the cystoscope and found the bladder large, easily holding seven ounces. The average daily output of urine was 25—30 ounces. There was some basal cystitis, with much trabeculation and sacculation. Pyelography showed considerable dilatation of both ureters (Fig. 2).

Fig. 1. Radiogram of Case 1 showing bladder and tortuous left ureter filled with solution of Sodium Bromide.

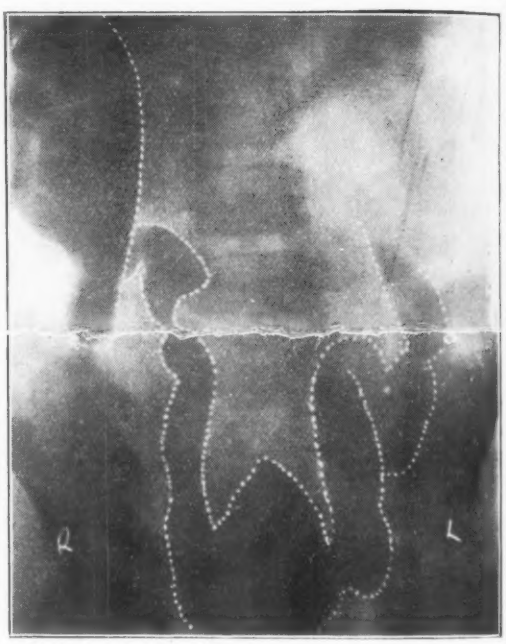

Fig. 2. Radiogram of Case 2 showing both ureters dilated and tortuous; the pelvis of the right kidney can be seen to be very dilated.

Seen three years later she had been in fair health, but suffered from constant thirst and was troubled by headaches and nocturnal frequency. There was a little puffiness under her eyes. The heart's action was forcible, and the cardiac dulness extended half a finger's breadth beyond the left nipple; systolic blood pressure 130 mm. The right kidney was just palpable. The urine was albuminous and contained much pus; blood urea was now 128 mgm. per 100 c.c. The patient is still under observation.

CASE 3. S. W., a boy, aged 2 years and 10 months, was admitted to hospital in January, 1926, for wasting. He had always been delicate and continually complained of thirst. On

admission the bladder was found reaching up t… …the umbilicus, and there was constant enuresis ; the urine was acid, contained a cloud of albu… …min and much pus, and on culture grew bacillus coli. Blood urea 104 mgm. per 100 c.c.

Experience of the former case of this ty… …pe led to cystoscopic examination of the bladder ; the bladder was distended, sacculated and … …rabeculated, and there was evidence of chronic cystitis ; the ureteric orifices were normal. … …nder the anæsthetic the right ureter was palpable but neither kidney was felt. Pyelography w… …s not attempted. As there seemed some slight obstruction at the level of the triangular ligar… …nt bougies were passed daily in sizes increasing from 6-10 to 10-14 and electrical treatment … …so employed.

In spite of treatment the bladder remained … …istended and the patient was discharged after 3 months in much the same condition as on ad… …ission. He is still under observation and the bladder has usually been found distended.

Case 4. E. M., a female child, aged 3 yea… …was admitted to the hospital in February, 1925, with a history of seven weeks' fever with … …igors and occasional vomiting. Previously to this she had been healthy and there was no hist… …y of enuresis. On the discovery of pus and albumen and bacillus coli in the urine, the diagn… …sis of acute pyelitis was made. Improving under medicinal treatment she was discharged, bu… …was again admitted in June, 1925, for a relapse with pus and albumen in the urine. This … …ime she was treated with an autogenous vaccine and again improved, but the urine still co… …tained a few pus cells. Again there was no history of enuresis. She was admitted a third ti… …me in June, 1926, and treated with citrate of potash and later with hexyl-resorcinol but recover… …y was only imperfect.

Re-admitted a fourth time in September, 1926, … …under Mr. O. Addison, cystoscopy showed a slight general cystitis. Pyelography showed the l… …ft kidney and ureter to be normal, but the right ureter was extremely dilated with a kink … …at the upper end. The renal pelvis was large but the calyces were apparently normal. Uri… …e from the left kidney contained urea 0.7%, a few red corpuscles but no casts ; from the rig… …ht, urea 0.5%, albumen, pus and tubular

Fig. 3. Radiogram of … …Case 4 showing a catheter passed up the right ur… …eter. The top of the catheter has reached … …a kink in the ureter.

casts, and from this the bacillus coli was grown. An X-ray examination of the urinary tract for calculus was negative. The radiogram by Dr. Bertram Shires shows the condition presented. (Fig. 3.)

CASE 5. I. M., a female child, aged 6½ years. In June, 1925, there was a history of an acute illness with fever and vomiting, and a diagnosis was made of acute pyelitis due to the bacillus coli. She was treated with a course of vaccines from July to November, 1925.

She was admitted to hospital in August, 1926, for losing weight since a febrile attack, and was found to have pus and albumen in the urine. The heart was normal; systolic blood pressure 115 mm. The right kidney was palpable and freely movable. The urine was pale, S.G. 1010, and contained pus and albumen, but no blood or casts. B. coli was isolated. Blood urea 42 mgm. per 100 c.c.

Urea concentration test:—

Before urea	2.11%
After urea 1 hour	1.78%
2 hours	2.39%
3 hours	2.27%

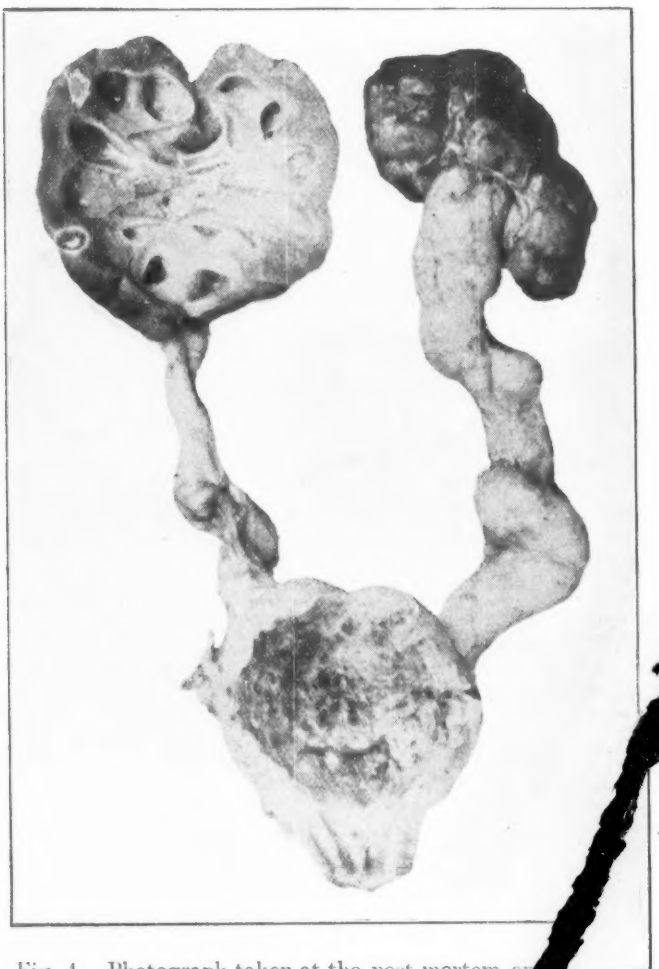

Fig. 4. Photograph taken at the post-mortem ex
of Case 6 showing hypertrophy of the bladder and
of the ureters. The urethra has been divided
the veru montanum.
amination
dilatation
st distal to

Cystosc… large and …

CASE … py showed the left ureteric orifice large, gaping and motionless. The right also was admi… drawn out. There was no inflammation.

incontin… For this case we are indebted to Mr. Tyrrell Gray. J. C. W., a boy, aged 15 months, healthy, …tted on June 15th, 1926, and died three days later. There had been a history of with s… nce of urine for about eight months. He was the elder of two boys, the younger being pus; … There was no history of miscarriages. The infant was very ill, grey and dyspnœic, were … gns of bronchopneumonia. The urine was alkaline, and contained much albumen and tio… on culture a micrococcus of the fæcalis alkaligenes group was isolated. The kidneys of … not palpable. Death rapidly followed from bronchopneumonia. Post-mortem examina-i… showed considerable thickening and sacculation of the bladder, and bilateral dilatation … the ureters with hydronephrosis; microscopically the kidneys showed some degree of chronic …terstitial nephritis. At the autopsy the urethra was divided immediately distal to the veru …montanum and a probe passed along the penile urethra met with no obstruction. The penile urethra was not, however, opened.

The photograph reproduces the condition post mortem (Fig. 4).

CASE 7. For this case we are indebted to Dr. Hutchison. A male child, aged 2 years, was admitted on February 24th, 1927, and died a month later. Since nine months old he had passed urine in a constant dribble both by day and by night, and throughout this period had been excessively thirsty; for the last year he had slowly lost flesh and for the last three weeks had suffered from persistent vomiting.

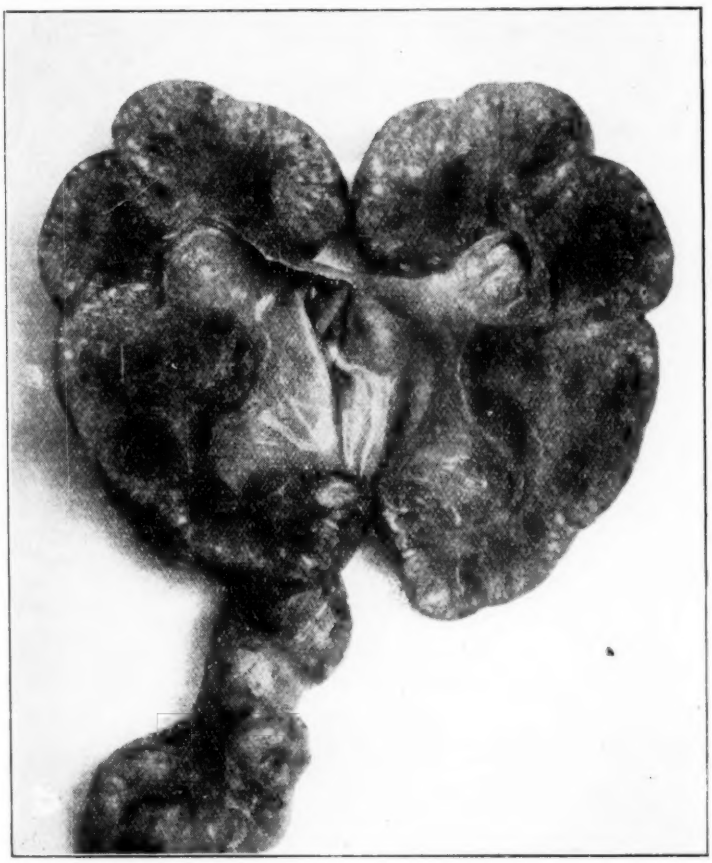

Fig. 5. From Case 7 showing the final state of the kidney. The cortex is riddled with small abscesses, a condition of suppurative pyelonephritis.

On admission, the child was ... tended, and on palpation the ... of the umbilicus. Urine cor... pale and undersized, weight 16 lbs. The abdomen was dis... the bed dry. The urine was ... dder could always be felt, generally reaching up to the level some pus; there were no cast... utly dribbled away so that it was found impossible to keep infantilism were not present. ...ale, specific gravity 1010, containing a trace of albumen and

Chemical analysis of the ...s or red blood cells. The bony changes associated with renal phosphorus (inorganic) 11 ... The heart was normal in size; systolic blood pressure 90-95 mm. tration in the urine after ... blood by Dr. G. A. Harrison, gave urea 109 mgm. per 100 c.c., was negative. ...ngm. per 100 c.c., calcium 7.8 mgm. per 100 c.c. The urea concen-

From the time of ... grammes of urea only reached 0.95%. The Wassermann reaction took no interest in his to... were accompanied by ... mission until death the boy was in a condition of chronic uræmia. He when his tongue beca... ys or surroundings, but lay very listless and drowsy. All his movements resulted from uræmi... fine uræmic tremor; vomiting was a symptom during the last week,

At the post-mo... ne very dirty and his lips were cracked and ulcerated. Death eventually The kidneys were l... .

...tem examination, apart from the urinary apparatus the body was normal. ...oth swollen, and were riddled with small abscesses (Fig. 5); on the surface

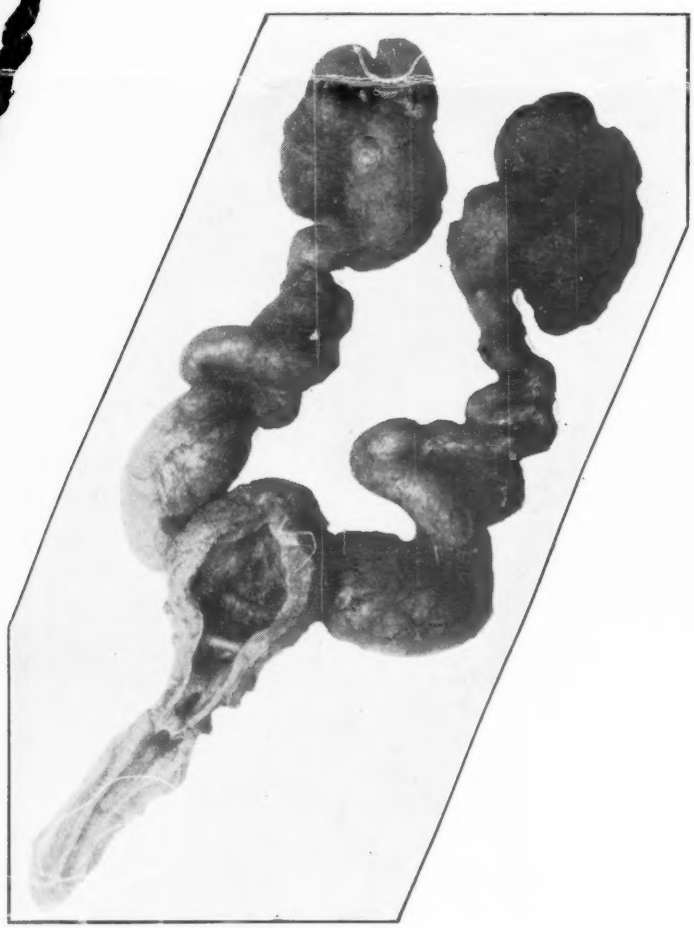

Fig. 6. Showing the whole urinary tract of Case 7. A dark probe has been passed beneath the valve in the posterior urethra.

of the kidneys were several small cysts, and the renal capsules were adherent in places. Microscopically, in addition to the abscesses, the kidneys showed some increase of interstitial tissue. Both renal pelves and their calyces were dilated, and contained urine turbid with pus. The ureters were both dilated and tortuous, the dilatation becoming more marked towards their lower ends. The ureteric orifices were normal. The bladder showed considerable hypertrophy of its musculature; although the vesical sphincter was quite prominent it did not appear to be more hypertrophied than the rest of the bladder. There were several petechial hæmorrhages under the mucosa of the bladder, the result of an acute cystitis. The prostatic urethra was considerably dilated, but beyond the level of the membranous portion, the urethra was normal.

The cause of the dilatation of the whole urinary tract behind the membranous urethra was found to be a valve-like structure formed by two folds of mucosa, which, taking origin from the distal end of the verumontanum swept round the sides of the urethra to fuse at the roof. From their line of fusion, there hung down a valve-like curtain of mucosa into the lumen of the urethra. The free edge of this valve was directed slightly towards the bladder, and offered an obvious obstruction to the outflow or urine (Figs. 6 and 7).

Fig. 7. Shows a larger view of the urethral valve (Case 7) with the probe in position beneath the valve. Note the thickness of the bladder musculature.

CASE 8. For this case we are indebted to Dr. Frew. A male child, aged 4 months, was admitted on March 24th, 1927, and died two days later. The child was brought to hospital for vomiting of two days' duration. He was the fourth child of a healthy family, and had previously been normal.

On admission the infant was pale and looked very ill. The urine was turbid and contained a heavy cloud of albumen, and microscopically was found to be crowded with pus cells. An X-ray photograph of the urinary tract showed nothing abnormal. The blood urea was 84 mgm. per 100 c.c. Treatment with potassium citrate was commenced, but on the day after admission the child had two convulsions, and died on the following day.

At the post-mortem examination, apart from the urinary tract the body was normal. The right kidney and right ureter were normal, and the ureteric orifices when viewed from the bladder appeared normal. The right ureteric orifice easily admitted a small probe, and urine could be expressed from the right ureter into the bladder. It was, however, found impossible to pass a probe from the bladder into the left ureter, nor could urine be squeezed into the bladder from the left ureter. The nature of the obstruction to the left ureter was only found after a careful dissection of the parts, when a narrow channel nearly half an inch in length was discovered leading from the dilated portion of the left ureter down to the ureteric orifice. This channel represented the terminal portion of the left ureter, and its lumen was too small to admit anything larger than a fine bristle.

The photograph shows the condition present (Fig. 8).

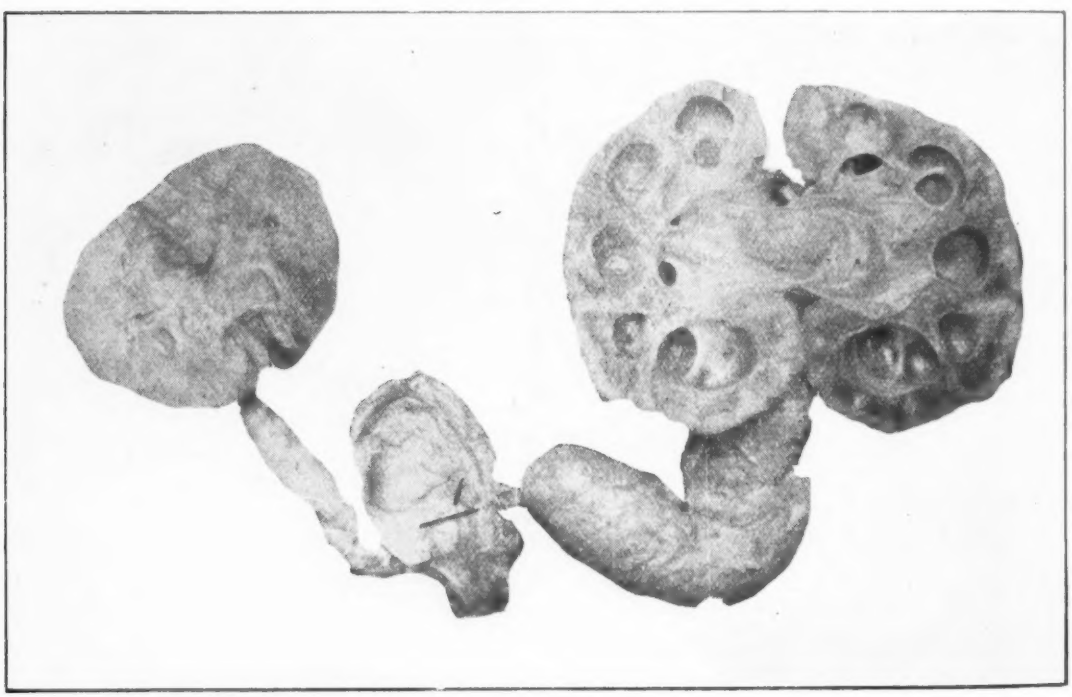

Fig. 8. Showing the condition present in Case 8. The left ureter is very dilated, except for the narrow terminal portion close to the bladder. Bristles have been passed through the ureteral orifices from the bladder.

Classification and Discussion.

The various pathological conditions in the preceding eight cases led us to investigate the post-mortem records of the Hospital for Sick Children, and in these were found twenty-four instances of dilatation of one or both ureters, associated in four cases with hypertrophy and dilatation of the bladder. Study of their clinical symptoms and correlation of them with the post-mortem findings, together with a reference to the cases reported in the literature, showed that the subject could be simplified by dividing the cases into four groups according to the gross pathological condition present and whether or not the cause was determinable.

Group 1. Hypertrophy and dilatation of the bladder with dilatation of both ureters resulting from some obvious obstruction in the bladder or urethra.

Group 2. Hypertrophy and dilatation of the bladder with dilatation of both ureters, but without any obvious obstruction.

Group 3. A normal bladder with dilatation of one or both ureters due to some obvious obstruction in the ureters.

Group 4. A normal bladder with dilatation of one or both ureters, but without obvious cause for the dilatation.

We have found no instance of a definitely hypertrophied bladder in which the ureters have been normal, nor an example in which, with a hypertrophied bladder, only one ureter has been dilated. Apparently when an obstruction arises of sufficient degree to produce hypertrophy of the bladder, both ureters soon become secondarily dilated.

Group 1.

Well recognised causes for this group, such as a vesical calculus or neoplasm, require no further explanation. These conditions in childhood do not commonly produce marked alterations in the urinary passages. There is, however, a specimen in the museum of the Hospital for Sick Children showing these results produced by a large vesical stone, and two similar examples resulting respectively from a myo-sarcoma and a papilloma of the bladder.

Other causes that have been cited as giving rise to obstruction to the passage of urine with secondary changes in the bladder, ureter and kidneys are congenital torsion of the penis, phimosis, atresia of the urethra, congenital hypertrophy of the veru montanum, cysts of the urethal mucosa and prostate, incomplete septa across the urethra, and valvular formations of the urethral mucosa. Valve formations have so far only been found in the male urethra and occur at the outlet of the bladder or in the posterior urethra.

Although many of the causes in this group are present at birth, in those cases that survive after birth symptoms may not appear for some months or years. The age of onset of symptoms is determined to some extent by the degree of obstruction, for obviously the most severe obstructions will tend to give rise to the earliest symptoms. In the milder cases puberty may be reached before the kidneys are sufficiently damaged for symptoms of chronic nephritis or uræmia to be manifest ; in others the symptoms of urinary infection may first appear and prove quickly fatal or else very resistant to treatment.

Enuresis is a common symptom and is generally first noticed at the time when the normal child should be gaining control of the sphincters. The enuresis differs from the more common nocturnal type in that the urine flows uncontrolled during both day and night. These children might be expected to suffer from painful spasm of the bladder in attempting to overcome the obstruction, but symptoms of pain and distress from the distended bladder do not arise; nor has the bladder been palpated while undergoing active contractions, although the height of the bladder above the symphysis certainly varies from day to day from being just palpable to reaching as high as the umbilicus. In cases in which it is possible to pass a catheter and empty the bladder, examination a few hours later will generally show that the organ has again become over-distended.

The ureters not only dilate but increase in length and may become very tortuous; the renal pelves become dilated, although in our cases they could not be palpated; the kidneys gradually undergo chronic interstitial inflammation and, as a result, the daily output of urine is excessive. The urine is pale and of low specific gravity. Eventually in most cases the urinary tract becomes infected with the bacillus coli producing cystitis and pyelitis, which in the fatal cases advances to suppurative pyelonephritis. In some of our cases the occurrence of pus in the urine has extended over several years. Case 2 has had pyuria for four years and is quite intractable to the ordinary lines of treatment. Death results from uræmia.

Group 2.

The symptoms of this group differ in no way from those of the preceding group except that the passage of a catheter should meet with no obstruction whereas in Group 1 it may be difficult or impossible to get a catheter as far as the bladder. In Case 7, the case with a valvular obstruction, the dilatation of the bladder was regarded as idiopathic until it was found impossible to get a catheter past the posterior urethra; the presence of a septum or valve in the prostatic urethra was then suspected and anticipated at the post-mortem examination.

A study of this case with Case 6 may throw some light on the causation of some of those instances hitherto regarded as idiopathic. Had the presence of a valve in the urethra in Case 7 not been suspected before performing the autopsy, it is probable that the kidneys, ureters and bladder would have been removed *en bloc*, the urethra being divided somewhere across the prostatic portion. Owing to the direction of the valve, had a probe then been passed up from the glans penis towards the bladder, the end of the probe could easily have negotiated the valve and thus the cause of the condition would have been missed. It is important therefore when performing an autopsy on this type of case *to remove the urethra in continuity with the bladder*, a proceeding which is facilitated in children because the symphysis pubis can be divided and the two halves widely separated to make the dissection of the urethra easy. At the post mortem on Case 6, the urethra was divided at the distal end of the verumontanum and although a probe was passed along the penile urethra, in

the light of the findings in Case 7, it is possible that some form of valvular obstruction may have been overlooked, or destroyed when the urethra was divided.

The passage of a probe along the urethra is generally taken as evidence that there is no obstruction, but it has been pointed out by previous writers that the free edge of a urethral valve formation is usually directed towards the bladder, and thus while egress of urine is prevented, a catheter or probe could pass up from the glans penis through the valve to the bladder. Moreover, the valve is composed of thin tissue which could easily be torn and destroyed if any slight force were used in passing a probe.

The only satisfactory way of proving an obstruction in the urethra post mortem is to remove the entire channel with the bladder. Even then unless the urethra is opened up cautiously a valve or incomplete septum may easily be severed ; it would then be difficult to appreciate the precise nature of the obstruction. These difficulties are well illustrated by four specimens of *idiopathic* dilatation of the bladder and ureters in the museum of the Hospital for Sick Children. In all of these the bladder has been severed at its junction with the urethra. In two there is no record of the examination of the urethra, and in the other two (one from a female child) the urethra is stated to have admitted a large probe ; but as has been pointed out, this does not necessarily exclude the presence of some organic obstruction.

The secondary changes that occur in the bladder, ureters, and kidneys in the second group are identical with those in Group 1, and there can be no doubt that these changes result from some form of obstruction. From the evidence of the specimens at our disposal we cannot eliminate from this second idiopathic group the possibility that an obstruction has been overlooked. In view of the minute examination required to discover such an obstruction as was present in Dr. Hutchison's case, and bearing in mind the anatomical similarity of the cases in Group 2 to those in Group 1, we are of opinion that there is no convincing evidence to enable us to set aside a mechanical explanation, which seems to fit the facts better than any other.

A study of the literature certainly indicates a group in which no obstruction has been discovered after death, and various theoretical explanations have been suggested to account for such cases.

They have been compared with hypertrophic pyloric stenosis. On anatomical grounds, we believe such a comparison is not strictly justifiable because in the majority of cases of idiopathic hypertrophy of the bladder the sphincter vesicæ has not been found hypertrophied out of proportion to the rest of the bladder as is the pyloric sphincter to the rest of the stomach ; indeed, it is usually found that the whole bladder is equally hypertrophied. A more suitable comparison has been drawn with congenital idiopathic dilatation of the colon, where part or the whole of the colon is thickened without special hypertrophy of its terminal portion. It still remains to explain the hypertrophy of the muscle.

It has been suggested that in certain instances where hypertrophy of the bladder has been associated with spina bifida or spinal disease, a defect in the nervous mechanism of the bladder has resulted from the spinal deformity. It is, however, conceivable that we have in such cases two different congenital abnormalities existing in the same child, just as congenital morbus cordis and mongolism often occur together, and that the spina bifida bears no direct relationship to the hypertrophy of the bladder. In the absence of any gross malformation or disease of the spinal cord, it is possible that there might be a congenital maldevelopment of the nervous control of the detrusor and sphincter muscles of the bladder, resulting in an inco-ordination of their reciprocal functions, so that the normal contraction of one and the simultaneous relaxation of the other would be replaced by simultaneous contraction or relaxation of both groups of muscles. Such a disharmony might lead to hypertrophy of the whole bladder.

The thickness of the bladder has been regarded in some instances as due to a primary developmental hyperplasia of the muscle ; but provided that the nervous control of this muscle is unimpaired, the mere fact of hyperplasia should not produce obstruction and incontinence.

The urine in our cases has been of low specific gravity and free of mucus, and could of itself offer no obstruction. Excess of mucus in the bladder has been described and brought forward as a possible cause of obstruction. At the post-mortem examination on two of our cases there was an intense hæmorrhagic cystitis, but no increase of mucus was noticed in the bladder.

Group 3.

The symptoms and morbid anatomy of this group bear scarcely any relation to those of the preceding groups. Many instances such as Case 8 show no symptoms during life to point to disease of the urinary system, and the condition is revealed unexpectedly at post-mortem examination. In others a bacillus coli infection occurs in the kidney, and if the patient survives for any length of time, the persistence of pyuria in spite of continuous treatment arouses suspicion that the case is more than a simple pyelitis. The need for examination with the cystoscope and investigation by means of pyelography become essential if the true state of these cases is to be elucidated. Even these means may fail in instances such as Case 8, where it would have been impossible to catheterise the stenosed lower end of the left ureter.

Dilatation of one ureter may be due to impaction of a calculus in the lower end of the ureter, or may result from a new growth. In the museum of the Children's Hospital are two specimens showing considerable dilatation of a ureter by impaction of a calculus. Other causes for obstruction consist of twists and kinks of the ureter, produced in some cases by aberrant renal vessels. Portions of the ureter may be severely narrowed, or the canal actually obliterated in part of its course.

Figure 9 shows a condition exactly analogous to Case 8, in which the left ureter is very dilated from stenosis of its terminal half inch. In Figures 8 and 9 the stenosed portion is obvious, but at the post mortem on these cases, the cause of the dilatation was obscured because the dilated ureter was adherent to the bladder and completely hid the terminal narrow canal; the stenosis extended down to but not through the bladder wall, so that the ureteric orifice into the bladder appeared normal. A complete dissection of the parts was necessary before the precise nature of the obstruction became apparent.

Fig. 9. A photograph of a specimen from the Museum of the Hospital for Sick Children, showing a condition of the left ureter precisely analogous to Case 8. The normal right ureter has been removed.

Such malformations are usually unilateral. Dilatation of both ureters due to some congenital abnormality in them must be very uncommon, but we have had one specimen in which both ureters were dilated to the size of intestine, although the bladder was normal. Further examination showed that the lumen

of both ureters at their lower end was very small, barely admitting a fine probe, and it is probable that the dilatation resulted from a bilateral stenosis of the ureters.

A curious association with dilatation of the ureters is that of horseshoe kidney, of which we have found three examples. In two, the left ureter only was enlarged, and in one of these the post-mortem record states that the lower end of the ureter was very narrow, only admitting a fine bristle. Figure 10 is a photograph of this specimen. In the third example, " both ureters were

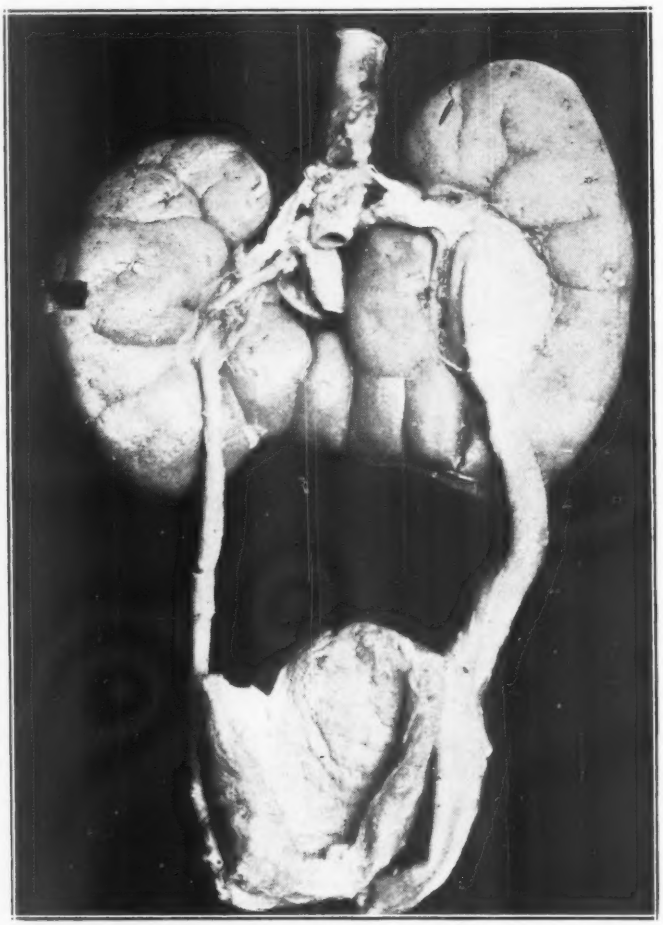

Fig. 10. A photograph of a specimen from the Museum of the Hospital for Sick Children, to show the association of horsesboe kidney with dilatation of the ureters. In this specimen, the left ureter only was dilated.

dilated resembling small intestine, and considerable pressure was required to force urine into the bladder." There can be no direct relation between horseshoe kidney and stenosis of the ureters, the association of the two conditions seems to be another instance of two congenital abnormalities existing in the same child.

Group 4.

In all the specimens of dilatation of one or both ureters in conjunction with a normal bladder that we have examined, there has been some form of congenital or acquired organic obstruction sufficient to account for the dilatation. Cases of megalo-ureter are recorded in the literature in which no organic obstruction has been found. In one such instance, recorded by Grant, a girl, aged 18 months, had had for three months a heavy deposit of pus in the urine. Pyelography showed both ureters sausage shaped, the dilatation extending to the renal pelves ; the bladder was normal and the ureteric orifices were patulous so that there was no discernable obstruction. The dilatation was considered to be secondary to infection which had in some way lowered the tone of the ureteric muscle. Treatment by irrigation of the bladder was performed four times a day for three months, by which time the ureters had become much smaller and their orifices practically normal.

Other instances have been explained on an embryological basis. It has been shown that between the fourth and fifth month of intrauterine development the ureters are of relatively large calibre, and a persistence of this after birth would result in a congenital megalo-ureter. A primary hypoplasia of the muscle of the ureter would aid in a persistence of the fœtal proportions, but in the dilated ureters which we have examined microscopically there has been no evidence of hypoplasia, the amount of muscle has been in excess of the normal.

The view that abnormal development of the nervous control of the ureters may take place in some cases, with the production of spasm of a segment of the ureter, the portion above eventually undergoing a secondary dilatation, lacks any convincing proof.

Conclusion.

Our conclusion from this investigation is that we believe there is in most of these cases of dilatation of the bladder and ureters in children a definite organic obstruction rather than a primary disturbance of function.

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GAUCHER'S DISEASE; A CLINICAL AND PATHOLOGICAL STUDY.

BY

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Splenic enlargement in infancy and early childhood is a common clinical finding but the diagnosis of its cause is often a problem of great difficulty. In the present communication, it is not our intention to discuss the merits of any classification, or the question of differential diagnosis, but rather to bring forward a series of cases illustrating a definite clinical entity, which has, as one of its cardinal signs, a splenomegaly, namely, Gaucher's disease.

In 1882, Gaucher (1) described the first case of the condition which bears his name, believing it to be an epithelioma of the spleen. It was not until thirteen years later that Collier (2) in this country and Picou and Ramond (3) in France described the next cases. In 1900, Bovaird (4) described the first of the American cases: he believed the large cells which are characteristic of the condition to be endothelial in origin. In 1904, Brill and Mandelbaum (5) reported the original case of their series, describing for the first time the occurrence of the large cells in the bone-marrow, and it is to these writers that we owe a considerable amount of our knowledge concerning the clinical and pathological nature of the disease. Since then, many cases have been recorded. Schlagenhaufer (6) reported the first of the German cases in 1907 and referred to it as a disease of the lymphatic-hæmatopoietic system. In 1919, Mandelbaum (7) stated that up to that time (1919), there were 21 undoubted examples in the literature, many more having been reported as such but discarded by him on the grounds of insufficient evidence. To this group of unproven cases belong those reported by Knox, Wahl and Schmeisser (8) as well as the two sisters reported by De Lange and Schippers (9). It is only fair to state that one year after their first publication, these last two authors again published a report (10) stating that their original diagnosis was incorrect. Pick (11), in 1926, collected 39 cases, 5 of which were seen and reported by him personally. He agrees with Mandelbaum in discarding certain cases in which the evidence in favour of Gaucher's disease was not complete. Of the 39 cases in his series more than half (22 as compared with 17) have been reported during the last seven years, that is, since Mandelbaum's series in 1919.

We have been fortunate in having had under our observation during the last three years, four cases of Gaucher's disease, and through the kindness of Mr. MacLennan, the spleen from a fifth case was obtained for pathological study.

REPORT OF CASES.

CASE 1. M.F., female, aged 18 months; only child; full-term baby, healthy at birth and breast-fed for one month, then dried milk till one year, and since then mixed diet. She cut her first tooth at seven months and was able to sit up at nine months. She had always been a pale baby. When 11 months old, she went off her food and became much paler. When

14 months old, it was noticed that the abdomen was becoming much larger. She was seen shortly afterwards by a physician who suspected abdominal tuberculosis and referred the case to hospital.

Physical Examination on Admission. A pale, wasted infant, weighing 7 kg. There was a faint but definite icteroid tint of the skin. In comparison with the chest the abdomen appeared to be greatly enlarged and on palpation there could be felt an enlarged spleen completely filling the left half of the abdomen, extending two centimetres to the right of the umbilicus and well below the iliac crest. The liver also was enlarged, the lower border being six centimetres below the right costal margin. The teeth were mainly decayed stumps, and the gums were spongy and bled readily. The examination revealed nothing otherwise relevant, the Wassermann reaction being negative, as also the v. Pirquet tuberculin test. The blood examination on admission was as follows :—

Hæmoglobin	20%
Red cells	2,090,000
White cells	8,600
Colour index	0·6
Differential count (of 200 cells) :—	
Polymorphonuclears	31%
Lymphocytes	62%
Eosinophiles	2%
Transitionals	3%
Myelocytes	2%

Slight anisocytosis and poikilocytosis were noted but no nucleated red cells were seen.

Progress. Five days after admission, the leucocytes numbered 4,800, remaining between 4,000 and 6,000 until death. The baby was transfused twice, 220 cc. being given on the first occasion and 260 cc. on the second. After each, there was considerable oozing of blood from the transfusion wound. There was occasionally slight irregular fever but for the most part the course was afebrile. After one month in hospital, the patient had lost weight, was refusing food and generally had lost ground. The blood examination at this time was as follows :—

Hæmoglobin	68%
Red cells	4,050,000
White cells	5,400
Colour index	1·0

The smears differed in no way from those previously described, except that the myelocytes numbered only 0·5 per cent. Two days later the baby suddenly collapsed and had a convulsion which ended fatally.

Post-mortem Examination. No gross lesion was found in the thoracic viscera. The bronchial and tracheal glands were not enlarged and the thymus was small. On examination of the abdomen, no ascites was present. The liver, which weighed 395 grm., was of a pale brownish colour, the cut surface showing a fine cirrhosis and mottling due to small pale areas being scattered throughout the substance of the organ and bearing no definite relation to the portal tracts. At places this pale tissue formed larger nodules about the size of peas. The naked-eye picture did not suggest a leukæmic infiltration and the cut surface gave a slight hæmosiderin reaction. The spleen was much enlarged and weighed 500 grm., its greatest length being 15 cm., and breadth 6·5 cm. There was no evidence of perisplenitis. The cut surface of the organ was of a greyish-brown colour and markedly mottled, the appearance being very like that of coarse sea-sand. The Malpighian bodies were not prominent and the cut surface gave a slight hæmosiderin reaction. The kidneys which together weighed 34 grm. were pale and showed a slight fatty change. The mesenteric and retro-peritoneal glands were enlarged, being mostly of the hæmolymph type. The largest glands (about the size of almonds) were found near the upper part of the mesentery. No evidence of tuberculosis was noted in any of these glands which were discrete, of a uniform consistence and pinkish in colour. No evidence of disease was found in the stomach or bowel, the lymphoid tissue in the latter structure showing no gross

change. No lesion was found in the bones of the skull, in the middle ears, or in the brain. The marrow of the femur appeared normal for a child of this age, though here and there throughout its substance small pale areas of the size of a pin's head were found.

Histology. On microscopic examination of the spleen the pulp spaces were found to be packed with large cells 20 to 40 μ in diameter with a clear protoplasm which on examination with a high power showed a finely reticulated appearance. The nuclei of these cells were small and stained darkly, occasionally a cell showing two or more nuclei being observed. Vacuolation of the protoplasm of the cells was rare and they seldom showed any phagocytosis of red cells and only an occasional mitotic figure was seen. Practically the whole of the splenic pulp had been replaced by these cells, the small sinusoids being pressed on and occasionally containing a large Gaucher cell (Fig. 1 and 17); the capsule of the spleen was not invaded. The Malpighian bodies were small, Gaucher cells being found in the peripheral parts of these structures as well as in the germ centres which had almost entirely been replaced by the large cells (Fig. 2). In places, masses of Gaucher cells were noted in the lumina of branches of the splenic vein (Fig. 3). A point to which Pick [12] draws attention was also seen in this case, namely, the occurrence of the Gaucher cells in the adventitial coat of the small vessels (Fig. 4). Pick suggests that the large cells may take origin from the adventitial cells but in the present series this was the only case in which the appearance was noted. The staining of these large cells by Mallory's method is very typical and serves as a quick method for picking out the cells in other tissues as the protoplasm stains bluish and shows a fine reticulum which is stained more by the fuchsin: this staining is looked upon as diagnostic by Epstein [13] who has investigated the disease chemically. These large cells were also in close relationship to reticulum (Fig. 5), and what appeared to be transition stages between Gaucher cells and reticulum cells and fibres were observed. A few of the cells showed a slight diffuse reaction for iron. No areas of necrosis or fibrosis were found in any of the sections examined. No glycogen was found in sections of tissue fixed in alcohol and cut in celloidin.

On microscopic examination of the liver a fine irregular cirrhosis was present, the area around the lobular branches of the hepatic veins being replaced by fine fibrous tissue and masses of Gaucher cells (Fig. 7) which were also found in the sinusoids between the remaining liver cells clustered around the portal tracts (Fig. 8). There was but slight proliferation of the bile ducts, while in places necrosis had occurred in masses of these large cells. It was only occasionally that a few Gaucher cells were found in the intra-hepatic branches of the portal vein, and invasion of the portal tracts (Fig. 6) was seldom noted. Another interesting feature of the disease in the liver was the small nests of cells clustered around very fine capillary vessels. The reticulated appearance of the cells was well marked in the liver, and some of the cells gave a slight diffuse reaction for iron. As in the spleen, a close relationship to reticulum on the part of these cells was noted (Fig. 9).

The lymphatic glands, noted to be enlarged at the autopsy, were found on examination to be of the hæmolymph type, Gaucher cells being scattered irregularly throughout their substance (Fig. 10). The large cells were not present in the peripheral lymph sinuses, such as one is accustomed to see in malignant disease with glandular metastases. A few Gaucher cells were found in the germ centres but this was not as marked as in the spleen. The cells gave no reaction for iron as did the spleen and liver, though, as in both these organs, they were still intimately associated with reticulum (Fig. 11).

On examination of the bone-marrow, small clusters of Gaucher cells, which were slightly smaller than in the other situations, were found, and these showed the same histological characters as in the situations already described (Fig. 12). Some of the large cells showed slight phagocytosis of the red cells and here again, as in the other tissues already examined, they were in close relation to reticulum (Fig. 13).

No Gaucher cells were found in sections of the lung, bronchial glands, kidneys, suprarenals, ovaries, Peyer's patches, pituitary, thyroid, thymus or superficial lymphatic glands.

Case 2. G.L., boy, aged 6 years, second child in family of four. This boy is a brother of R.L. (Case 3). None of the other members of the family was noted to have an enlarged spleen. He was a full term infant and throve and developed normally. When four years old he had

measles and whooping-cough. For 18 months previous to admission he had complained of tiredness on exertion and had been very constipated.

Physical Examination on Admission. A fair-sized boy with adenoid facies and marked frontal bossing. The abdomen was full and the spleen was enlarged, the lower border being palpable 4 centimetres below the costal margin. The lower border of the liver was 8 centimetres below the right costal margin. The teeth were very bad, and the gums spongy and bled readily. Otherwise the physical examination revealed nothing of significance. The blood examination was as follows:—

Hæmoglobin	58%
Red cells	3,540,000
White cells	5,700
Colour index	1·0

In films no abnormal cells were seen. The Wassermann reaction was negative and the v. Pirquet test positive. There was no appreciable rise in the blood sugar after the ingestion of lævulose. Splenic tissue was obtained by means of puncture and the clinical diagnosis of Gaucher's disease confirmed on histological examination.

Progress. No appreciable change in the child's condition took place during his residence in hospital. There was no fever and, on the whole, the boy could not be considered ill. Four weeks after admission he was transferred to the surgical wards where splenectomy was successfully performed. At the operation it was noted that the liver was of a brownish colour and showed a slight cirrhosis: no piece was obtained for microscopic examination.

Pathology. Tissue obtained by Splenic Puncture. In films made from this material and stained with hæmatoxylin and eosin, many large cells were seen with a clear protoplasm in which a slight granular appearance could be made out and which contained one or more nuclei (Fig. 20). The size of the large cells as compared with the red cells is well seen in the figure. Paraffin sections were made as is afterwards described, and on examination showed small pieces of splenic tissue in which the pulp spaces were packed with large Gaucher cells (Fig. 19).

Spleen. The cut surface of the spleen immediately after removal was of a reddish-brown colour, the Malpighian bodies being prominent though widely separated from each other. The capsule was smooth. The organ weighed 230 grm., its greatest length being 14 cm. and breadth 4 cm. On histological examination of the spleen, the cellularity of the organ was not as marked as in the first case. The Malpighian bodies were larger than usual, the enlargement being due chiefly to a hyperplasia of the germ-centres in which a few Gaucher cells were present (Fig. 14). The Gaucher cells were similar in their characters and relations to those of the first case, but there was no invasion of the adventitial coat of the blood vessels and none of the cells gave a reaction for iron. Gaucher cells were seldom found in the lumina of the branches of the splenic vein. In this case the relationship of the cells to reticulum was particularly close, especially in the Malpighian bodies, where the appearance suggested that the cells were arising from reticular cells.

CASE 3. R.L., boy of ten years, oldest in family of four, healthy at birth and throve well in infancy. During the second year of life he had several attacks of diarrhœa, and at 3 years measles followed by otitis media which lasted for several years. At four years of age, he had chicken-pox, at seven years and again at eight years, pneumonia. His tonsils were removed after the second attack of pneumonia. For six months previous to admission he suffered from diarrhœa and often complained of pain in the left side of the abdomen. His mother noticed that he tired easily and became short of breath on the slightest exertion. For three months the pain in the side had been much worse and it was for this complaint that medical advice was sought.

Physical Examination on Admission. A fair-sized boy with adenoid facies and well-marked pigeon breast. The fingers and toes were clubbed and cyanosed. The abdomen was large and on the left side the spleen extended down to the iliac crest and across the abdomen to within two centimetres of the umbilicus. The lower border of the liver was eight centimetres below the right costal margin. Examination of the heart and lungs showed nothing abnormal to account for the cyanosis and clubbing of the fingers. The teeth were carious and the gums

were spongy and bleeding. The lips also bled readily. The blood examination on admission was as follows :—

Hæmoglobin	82%
Red cells	6,740,000
White cells	6,600
Colour index	0·75
Differential count :—	
Polymorphonuclears	64·5%
Lymphocytes	31·5%
Transitionals	3·1%
Myelocytes	0·9%

There was no abnormality in shape or staining of the red cells and their fragility was not increased The Wassermann reaction was negative. There was no rise in the blood sugar after the ingestion of lævulose and no rise in the leucocytes after the ingestion of protein (milk).

Progress. The condition did not alter during residence in hospital. There was no complaint of pain in the side but the patient was confined to bed. After the extraction of some carious teeth difficulty was experienced in controlling the oozing of blood from the gums. After one month in hospital he was transferred to the surgical ward for splenectomy, which was performed successfully a few days later.

Pathological Report. The spleen, received immediately after operation, weighed 744 grm., its greatest length being twenty centimetres and breadth, eight centimetres. The organ was of a brownish colour and the capsule was smooth. On cutting into the organ, the cut surface showed the Malpighian bodies widely separated from each other by a reddish-brown homogeneous soft pulp.

Histology. On microscopic examination the lesion in the spleen was not as cellular as in the second case though the histological picture was much the same except that the Malpighian bodies were not so hyperplastic (Fig. 15), and in these situations the Gaucher cells were found in very close relation to the reticulum.

Case 4. M.S., girl of ten years; family history negative; healthy at birth and breast-fed until ten months of age. With the exception of measles at three years and whooping-cough at five years, she was apparently well until fourteen months previous to admission, when she had a febrile illness accompanied by jaundice which was looked upon by her physician as pneumonia. All signs and symptoms cleared up except the jaundice. During the fourteen months she had two similar attacks, each lasting from a fortnight to three weeks. Between the attacks she seemed to be perfectly well, and though jaundiced, attended school.

Physical Examination on Admission. A well-developed and well-nourished child with a definite yellowish tinge of the skin and conjunctivæ. The mucous membranes were of good colour. The teeth were carious, and the gums were spongy and bled readily. The abdomen was large, due to the size of the spleen which was palpable eight centimetres below the left costal margin. The liver was palpable two finger breadths below the right costal margin. The examination otherwise revealed nothing of note.

The Wassermann reaction was negative. The v. Pirquet tuberculin test was positive. The blood examination was as follows :—

Hæmoglobin	62%
Red cells	3,520,000
White cells	6,400
Colour index	1·0
Differential count :—	
Polymorphonuclears	62·0%
Lymphocytes	31·3%
Large Mononuclears	1·6%
Mast cells	1·0%
Transitionals	3·0%
Myelocytes	1·0%

The size and staining of the red cells were normal, no nucleated red cells being present. The fragility of the red cells was within normal limits. The stools varied in colour, being at times distinctly like those of catarrhal jaundice, yet the urine was on all occasions free from bile although it contained a considerable amount of urobilin. The blood contained 2·5 units of bilirubin and the Van den Bergh test gave a biphasic reaction. The blood sugar rose from 0·112 per cent. to 0·136 per cent., one hour after the ingestion of fifteen grm. of lævulose. There was no rise in the leucocyte count after the ingestion of protein. After a period of two weeks in hospital, splenectomy was performed.

Pathological Report. The spleen, obtained immediately after operation, weighed 383 grm., its greatest length being 15 cm. and breadth 4.5 cm. The organ was of a brownish colour and the capsule was smooth. The cut surface differed from that seen in the three preceding cases, the Malpighian bodies not being prominent, and scattered through the reddish-brown pulp were numerous firm reddish areas suggestive of young connective tissue with softer yellowish-grey areas of necrosis. These areas were usually small and were not observed immediately under the capsule.

Histology. On microscopic examination there was present a greater degree of cellularity than in the case of the spleen of the two brothers, G.L., and R.L., but not to such an extent as in the first case, M.F. It is of interest to note that more multinucleated Gaucher cells were seen in sections in this case than in any of the others. The Malpighian bodies were still present and showed Gaucher cells in their peripheral portions and in their germ-centres. In addition, early fibrosis was present in places, the Gaucher cells no longer lying in the typically round pulp spaces (Fig. 16), but arranged in long columns between strands of fibrous tissue. At other places areas of more advanced fibrosis in which no Gaucher cells could be made out were present, such patches being chiefly in relation to vessels, the adventitial coats of which showed much fibrous thickening (Fig. 16). Areas of necrosis were also scattered throughout the sections and around these fibrosis was taking place. There were no Gaucher cells found in the thickened adventitial walls of the blood-vessels, though in the lumina of some of them a few Gaucher cells were present. The Gaucher cells near the areas of fibrosis and necrosis showed a slight diffuse reaction for iron while the endothelial cells lining the small sinusoids showed darker blue iron pigment which was in the form of small granules. The relation of the Gaucher cells to the reticulum was still close though this structure was becoming thicker and at places showed a deposit of collagen.

Case 5. Miss R., aged 38 years. During the examination of the patient on account of a suspected chest condition the spleen was noted to be greatly enlarged, the free border extending about two centimetres to the right of the mid-line. The liver was slightly enlarged. It was also observed that the fronts of both legs were pigmented as if habitually scorched. Further details regarding the history are not available ex ept that the patient's sister also has an enlarged spleen which, however, has never caused her any inconvenience. Splenectomy was successfully performed by Mr. MacLennan.

Pathological Report. The spleen weighed 2,495 grm. Its naked-eye appearance was similar to that in the last case although the fibrotic and necrotic areas were larger.

Histology. On microscopic examination the sections were less cellular as compared with the preceding case, the Malpighian bodies were still present, however, and Gaucher cells were found in their peripheral portions and germ centres. Large areas of fibrosis with hyaline and calcareous change were irregularly scattered throughout the sections, some of the blocks showing very little Gaucher tissue (Fig. 18). The adventitia of the vessels was greatly thickened and in general the fibrosis, as in Case IV, started in relation to the vessels, except in areas where necrosis had occurred in masses of Gaucher cells. The iron reactions and reticulum staining were similar to those of the preceding case.

Symptomatology.

Owing to the comparative rarity of Gaucher's disease the clinical manifestations have been considered more or less in detail.

Familial Nature. Collier [2] first reported the occurrence of this disease in more than one member of the same family. The case recorded by him was that of a boy who died at the age of six years and whose sister had died several years previously of a similar type of splenic enlargement. Although this case is accepted from the histological picture described as being that of Gaucher's disease, no reference is made by Collier to Gaucher's original description. Pick [11] states that in one-third of the reported cases, there has been a history of more than one child in the family suffering from the disease. So far, however, no case has been reported in which either parent was affected. Case 2 and Case 3 of this series are brothers and in the fifth case, as has been mentioned, a sister is also probably suffering from a similar condition.

Sex Distribution. The condition is slightly more common in females. Of forty-four reported cases, including the five detailed above, the disease is found to have occurred in twenty-eight females and sixteen males.

Onset. The onset is probably always insidious. Often the discovery of the splenic enlargement is made during the routine examination of the patient for some complaint in no way associated with the splenomegaly (Cases 2 and 5), or, as in Case 1, medical advice may be sought because of the steadily increasing size of the abdomen. Pain in the left side (Case 3) has also been frequently described and is said to be due to a localised perisplenitis, but in some cases it might be more correctly described as discomfort due to the size of the tumour. Also, some cases have come under the notice of the surgeon because of pathological fractures of the long bones.

Age at Onset. As the onset is insidious, it is impossible in many cases to state exactly when the condition began. In Case 1, the mother stated that the patient was always a pale baby, although when eleven months old she became much paler. In Cases 2 and 3, it is impossible to say when the trouble started, and especially is this so in the case of R. L. (Case 2), in whom the enlargement was discovered during a routine examination. In Case 4, the condition had apparently begun fourteen months previously. Although Gaucher's disease is said to begin in early childhood, it would appear that a diagnosis is not usually arrived at until a much later period in life. Of 44 cases, only 18 were under fifteen years of age when they first came under observation, and in 19 cases, the age was thirty years or over. The youngest case reported is that of an infant of eight months who died of broncho-pneumonia and enteritis. Two cases have been reported at the age of one year. M. F. (Case 1) eighteen months old, is the next youngest. Pick has recorded the occurrence of the condition in two brothers, aged 45 and 56 years. When one remembers that the disease is not, at least for many years, crippling, and in the majority of cases never interferes with the patient's work, it is readily understood why the diagnosis is not made earlier.

Spleen and Lymph-glands. Splenic enlargement in Gaucher's disease is always present and is slowly progressive. At times it may assume tremendous proportions as in Case 1, where the weight of the spleen was 500 grammes in a child weighing seven kilogrammes. In the case reported by Collier, the actual weight of the spleen was 4 lb. 2 oz. in a child weighing 23 lb.—roughly one-sixth

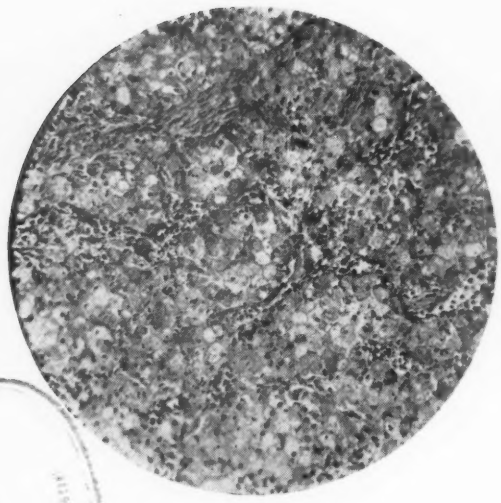

Fig. 1.

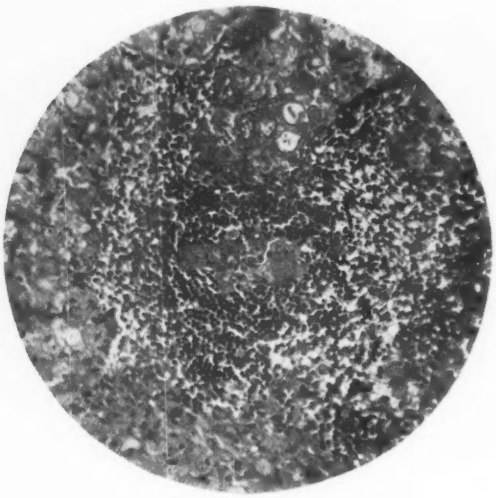

Fig. 2.

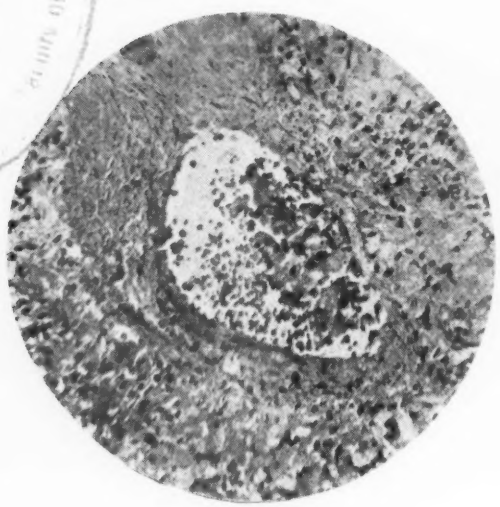

Fig. 3.

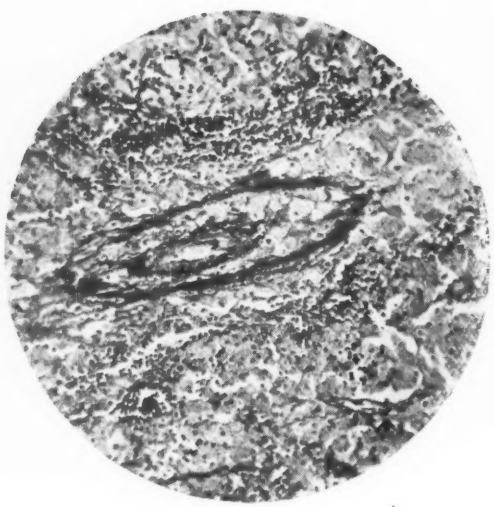

Fig. 4.

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Fig. 1.—Section of Spleen from Case 1 (M.F.).

The pulp spaces are seen to be packed with large cells which have a clear protoplasm and a small, darkly-staining nucleus. The venous sinuses are pressed upon and some contain a few large cells. (Iron hæmatoxylin.)

Fig. 2.—Section of Spleen from Case 1 (M.F.).

The germ centre of the Malpighian body, which is small, has been replaced by Gaucher cells. (Hæmatoxylin and Eosin.)

Fig. 3.—Section of Spleen from Case 1 (M.F.).

A clump of Gaucher cells is noted in a vein in the substance of the spleen. (Hæmatoxylin and Eosin.)

Fig. 4.—Section of Spleen from Case 1 (M.F.).

Numerous Gaucher cells are observed in the adventitial coat of a small vessel in the substance of the spleen. (Iron hæmatoxylin.)

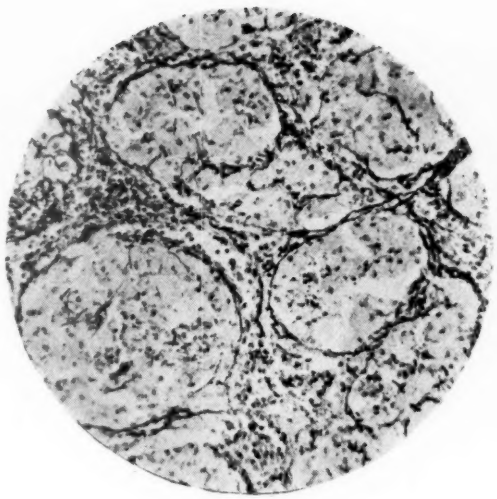


FIG. 5.

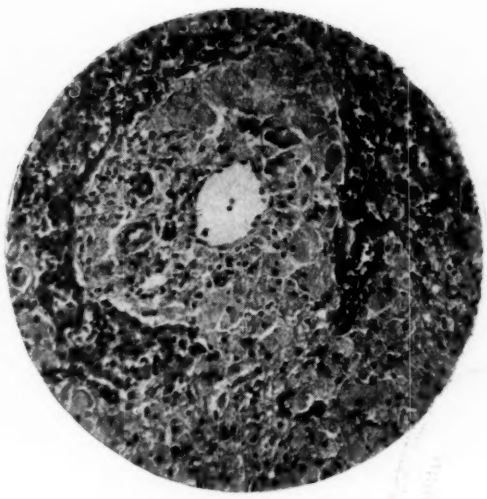


FIG. 6.

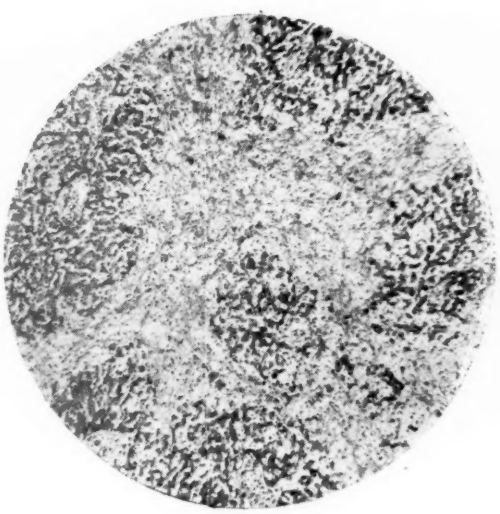


FIG. 7.

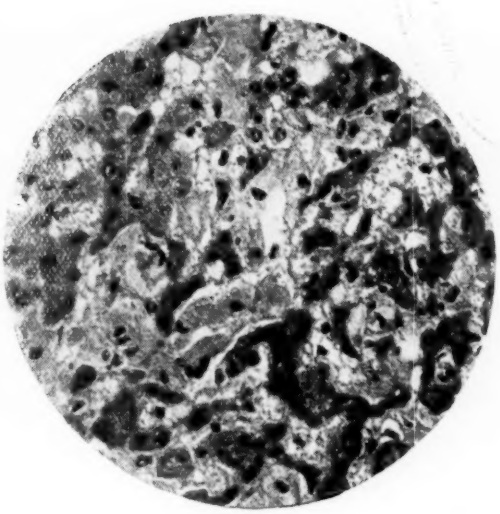


FIG. 8.

FIG. 5.—SECTION OF SPLEEN FROM CASE 1 (M.F.).

The section has been stained by Bielschowsky's method and shows darkly-staining reticular fibres surrounding the pulp spaces, the Gaucher cells being in intimate relationship to numerous fine fibres which run into the spaces.

FIG. 6.—SECTION OF LIVER FROM CASE 1 (M.F.).

Numerous large cells are seen in a small portal tract. (Hæmatoxylin and Eosin).

FIG. 7.—SECTION OF LIVER FROM CASE 1 (M.F.).

Gaucher cells and fine fibrous tissue are seen replacing the central portions of the liver lobules, the remaining liver cells being clustered around the portal tracts. (Iron hæmatoxylin.)

FIG. 8.—SECTION OF LIVER FROM CASE 1 (M.F.).

A high power view showing the large Gaucher cells in the liver sinusoids. (Hæmatoxylin and Eosin.)

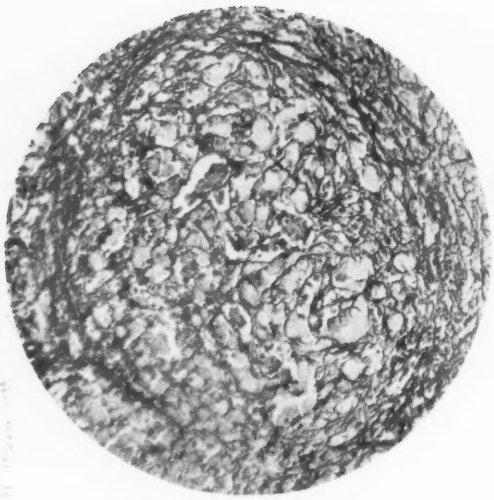


FIG. 9.

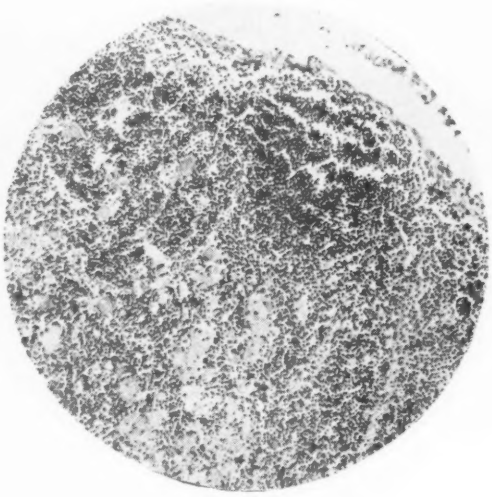


FIG. 10.

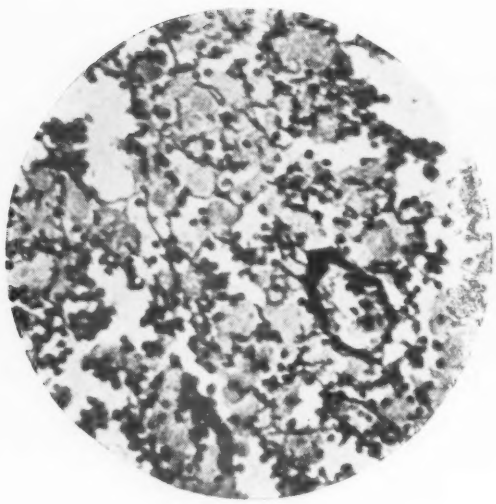


FIG. 11.

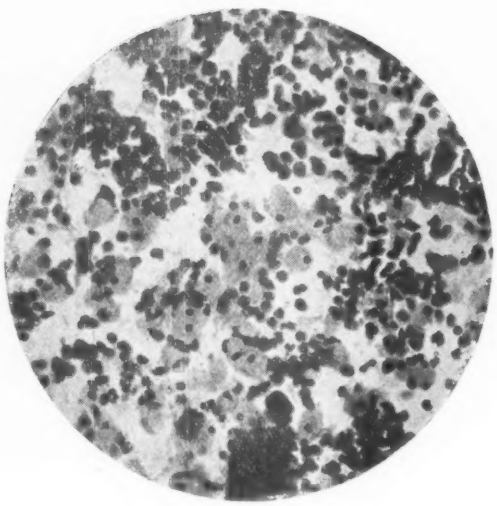


FIG. 12.

FIG. 9.—SECTION OF LIVER FROM CASE 1 (M.F.).

The section has been stained by Bielschowsky's method and shows the hyperplastic reticulum which is in intimate relationship to the Gaucher cells and in places completely surrounds single cells.

FIG. 10.—SECTION OF MESENTERIC GLAND FROM CASE 1 (M.F.).

The large cells are seen to be scattered throughout the substance of the gland; the peripheral sinus is free. (Hæmatoxylin and Eosin.)

FIG. 11.—SECTION OF MESENTERIC GLAND FROM CASE 1 (M.F.).

The section has been stained by Bielschowsky's method and shows the large Gaucher cells in close relationship to the darkly-staining reticular fibres.

FIG. 12.—SECTION OF BONE MARROW FROM CASE 1 (M.F.).

A clump of Gaucher cells is seen in the substance of the marrow. (Hæmatoxylin and Eosin.)

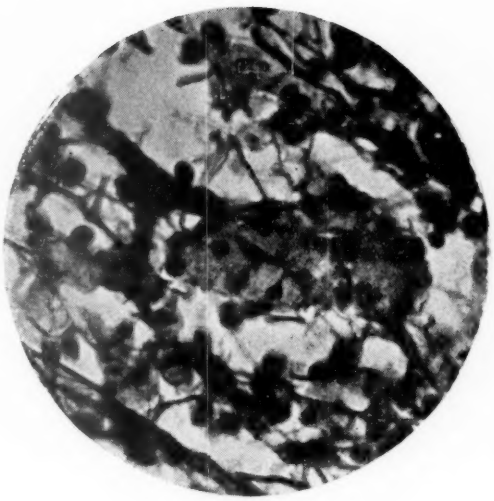
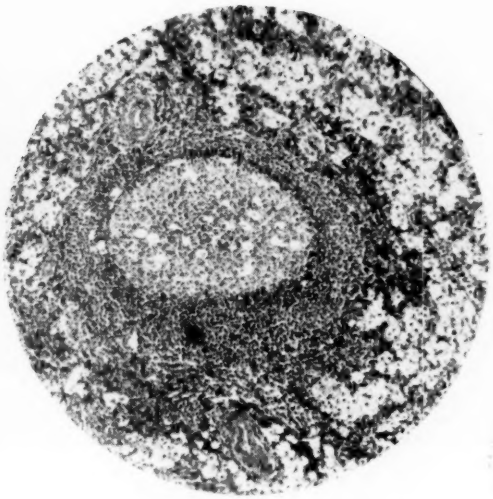


FIG. 13.



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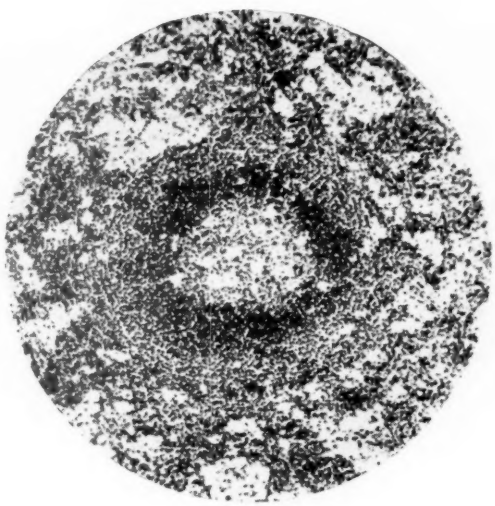

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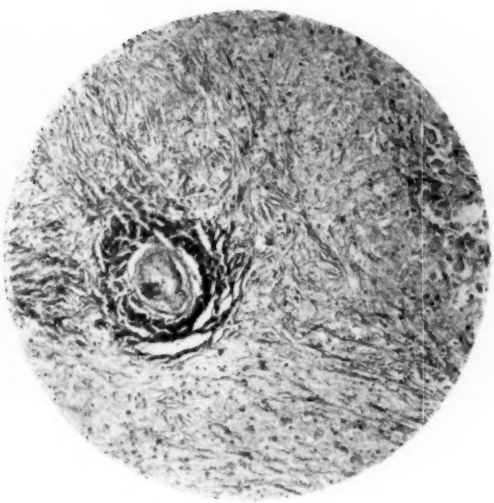

FIG. 16.

FIG. 13.—SECTION OF MARROW FROM CASE 1 (M.F.).

The section has been stained by Bielschowsky's method and shows the close relationship of large cells to the reticulum.

FIG. 14.—SECTION OF SPLEEN FROM CASE 2 (G.L.).

The Malpighian bodies are seen to be markedly hyperplastic and numerous Gaucher cells are present in the germ centres and in the surrounding zone of lymphocytes. (Hæmatoxylin and Eosin.)

FIG. 15.—SECTION OF SPLEEN FROM CASE 3 (R.L.).

The Malpighian bodies are not so hyperplastic as in Case 2; Gaucher cells are seen in the germ centres and surrounding zone of lymphocytes. (Hæmatoxylin and Eosin).

FIG. 16.—SECTION OF SPLEEN FROM CASE 4 (M.S.).

Marked increase of fibrous tissue is noted around the small vessel and radiating out from this into the masses of Gaucher cells are strands of fibrous tissue. (Hæmatoxylin and Eosin.)

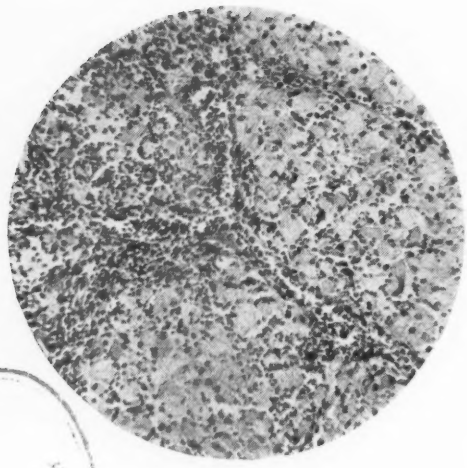

Fig. 17.

Fig. 18.

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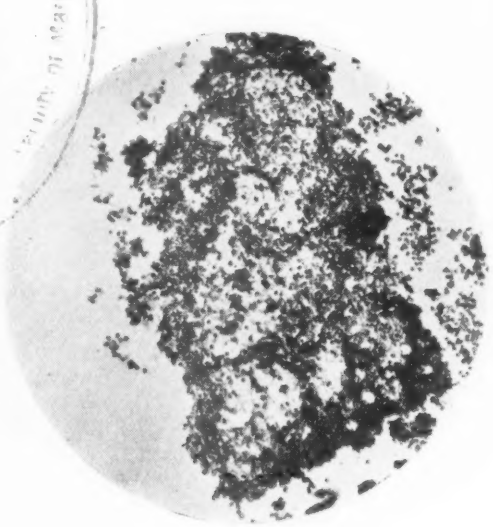

Fig. 19.

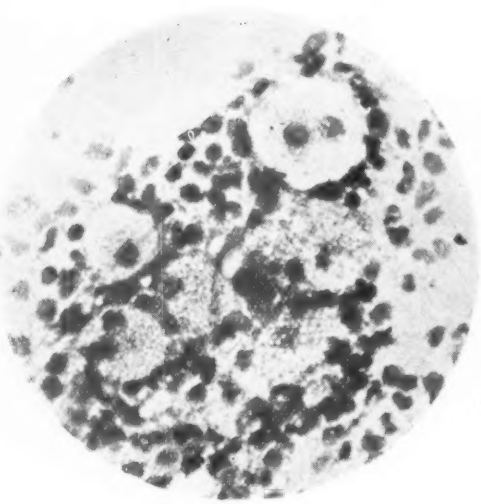

Fig. 20.

Fig. 17.—Section of Spleen from Case 1 (M.F.).

The pulp spaces are packed with Gaucher cells, a few of which are seen in the small sinusoids. Compare the appearance of this section (from a young child) with that of Fig. 18 (from an adult). (Mallory's stain.)

Fig. 18.—Section of Spleen from Case 5 (Adult).

Dense irregular fibrosis is seen throughout the section though numerous clumps of Gaucher cells are still present. (Iron hæmatoxylin.)

Fig. 19.—Section of Material Obtained by Splenic Puncture from Case 2 (G.L.).

A small piece of splenic tissue is seen in which numerous Gaucher cells are present in the pulp spaces. (Hæmatoxylin and Eosin.)

Fig. 20.—Film of Material Obtained by Splenic Puncture from Case 2 (G.L.).

A few large cells, some of which have more than one nucleus and showing a reticulated appearance of their protoplasm, are noted. The figure shows the size of the large cells as compared with the small, darkly-staining red blood cells. (Hæmatoxylin and Eosin.)

of the body-weight instead of 1/400. Enlargement of the superficial lymph-glands does not, as a rule occur, but it is of interest to note that those in the thorax and abdomen are usually enlarged, the extent of their enlargement depending on the degree of the involvement by the Gaucher cells.

Liver. A moderate enlargement of the liver is almost constantly present and this is of great importance in view of the similarity of Gaucher's disease to Banti's disease where, except in the early stages, the liver is small. Mandelbaum, however, has reported one fatal case in which the liver was not enlarged. In this case, also, there was no leucopenia, and ascites was present. The diagnosis was confirmed by histological examination, Gaucher cells being found in both liver and spleen.

Blood. There is no more constant feature in Gaucher's disease than the leucopenia which appears early and persists throughout. Excepting the anomalous case just mentioned, it has been present in all the published cases. Regarding the types of leucoytes present, there is nothing characteristic of the disease, although it is common in our experience to find a small percentage of myelocytes. As a rule the red cells are not greatly diminished, no nucleated red cells are present, and anæmia cannot be said to be a feature although there does occasionally occur an anæmia of the chlorotic type which may be very severe (Case 1). The fragility of the red cells is unaltered. There appears to be a definite tendency to hæmorrhages, especially from the mucous membranes (epistaxis, bleeding gums, bleeding lips, etc.), and in all of our cases this was very noticeable. In two of the cases there was considerable difficulty in controlling bleeding after the removal of carious teeth, and in Case 1, oozing of blood from the transfusion wound at the ankle persisted for several days. Unfortunately, the clotting time was determined in only one instance (Case 2), where it was found to be 128 seconds, the normal with the method used being 100 seconds.

Skin and Eyes. A brownish-yellow discolouration of the skin limited to the exposed parts has frequently been described, but is often absent. In one of our cases (Case I) the skin had an icteroid tint such as is usually seen in patients suffering from a severe anæmia. In another case (Case IV) there was a definite jaundice and in Case V pigmentation of the skin over the fronts of both legs was observed. In the others, no discolouration of the skin was noted.

Many writers have reported the presence of a brownish-yellow wedge-shaped thickening of the conjunctivæ affecting first the nasal side and later the temporal side. Brill and Mandelbaum (14) state that they have never seen a case in which it was absent. In our cases, although looked for carefully, it was never detected.

Later Manifestations. Pain of a dragging nature may be present and is said to be due to the weight of the enlarged spleen. Pain in the splenic region and localised areas of tenderness over the splenic tumour may occur, and are due probably to areas of perisplenitis. After many years there is often obtained a history of pain in the ends of the long bones, especially the lower ends of the femora, and pathological fractures have frequently occurred.

Course. The disease is in the majority of instances chronic and slowly progressive, although a fatal termination may ensue at a comparatively early age (*cf.* Case I). Schlagenhaufer's [6] patient lived for 37 years after the diagnosis had been made, and Brill and Mandelbaum [14] in 1913, refer to a sister of one of their cases in whom the disease is known to have existed for 24 years. The last writers give the average duration of life as 19½ years, but such a figure can only be a very rough approximation. Regarding the course of the disease after splenectomy, there seems to be no definite proof that the life of the patient is prolonged by the operation, although in many cases the symptoms of pain and discomfort are relieved.

Diagnosis.

It is probably unnecessary here to comment on the possibility of confusion in diagnosis between Gaucher's disease and such conditions as leukæmia, Hanot's cirrhosis, pernicious anæmia, tuberculosis and Hodgkin's disease. Special attention to the blood examination, the superficial lymph-glands, and the course of the disease will in the majority of cases serve to differentiate these conditions from Gaucher's disease.

The association of a splenic enlargement and a leucopenia, however, in an infant or a child should always suggest the possibility of Gaucher's disease to the clinician, but it must also be remembered that Banti's disease, particularly in the early stages, may present a picture so similar that from the clinical findings alone, it may be impossible to differentiate between the two conditions. Both maladies are associated with splenic enlargement and leucopenia. Banti's disease is not familial, does not appear before the beginning of the second dentition, and as a rule runs a more rapid course. The liver, except in the early stages, is not enlarged, and jaundice and ascites are of common occurrence. Furthermore, an anæmia is a much more distinctive feature of Banti's disease than of Gaucher's disease. Profuse gastric hæmorrhages from œsophageal varices are of frequent occurrence in Banti's disease but in Gaucher's disease, although bleeding from mucous membranes occurs frequently, large hæmorrhages are rare.

Certain cases of acholuric jaundice in children may also cause confusion in diagnosis, especially those cases in which there occurs a leucopenia. A history of erythroblastic blood crises with the rapid development of anæmia aids in the differentiation of the two conditions but the absolute diagnosis of acholuric jaundice rests on the detection of the increased fragility of the red cells. This fragility is unchanged in Gaucher's disease.

Splenic Puncture. If there is doubt or if confirmation of the diagnosis is wanted, valuable information may be gained by obtaining splenic tissue for histological examination by means of splenic puncture. This procedure was first employed by Bernstein [15] in 1915 to diagnose Gaucher's disease but apparently has not come into general use, although the method would seem to be devoid of danger. We have employed it on several occasions, and in conditions other than Gaucher's disease, with no untoward results.

The method adopted is as follows:—Having fixed the spleen firmly against the lower border of the ribs, a large bored needle with syringe attached is plunged into the substance of the spleen and a portion of splenic tissue sucked up into the bore of the needle in much the same way as a sample of cheese is taken. The needle is then withdrawn while still keeping up a negative pressure in the syringe. As a precautionary measure, a sterile swab is held over the site of puncture and firm pressure applied for a few minutes. The contents of the syringe and needle are now diluted with 6 to 8 cc. of distilled water to lake the red cells, and the whole gently washed into a centrifuge tube which is now spun at a low speed to get all the cells and pieces of splenic tissue to the bottom. A small amount of this sediment is pipetted off and from this films are made and fixed in formalin, after which they are stained by hæmatoxylin and eosin (Fig. 20) and in suspected cases of Gaucher's disease or Niemann's disease by one of the fat stains. Sufficient formalin is now added to the material left in the tube to make a concentration of approximately 10 per cent., which causes a fairly good coagulum to form. After the usual dehydration and clearing processes, the deposit is embedded in paraffin; all these steps are carried out in the centrifuge tube which, when the paraffin has set, is broken and the block removed. Ribbons are cut and every tenth section is stained and examined for splenic tissue (Fig. 19).

Pathogenesis.

Gaucher, when he originally described this disease, considered it to be of the nature of a tumour primarily of splenic origin. Collier, likewise, held this opinion and inclined to the view that the condition was an endothelioma. The Morbid Growths Committee of the London Pathological Society, however, to whom Collier submitted his preparations decided that the lesion was not a tumour and called attention for the first time to the fact that the lymphatic glands were also affected. About this time, also, Cornil [16] stated that the lesions described by Gaucher could not be a primary endothelioma, and expressed the opinion that it was a primary hypertrophy of the spleen with proliferation of reticular tissue.

The outstanding characteristic of Gaucher's disease is the presence of large cells with darkly staining nuclei, occasionally multiple, and with a finely reticulated protoplasm, found in all the tissues and organs in which the reticulo-endothelium is prominent, namely, spleen, liver, lymph-glands and bone marrow. The wide-spread occurrence of the cells throughout the substance of the lymphatic glands rather than masses of cells in the peripheral sinuses is more typical of a system disease than of a tumour. In some cases the spleen has been little affected, the lesions being chiefly in the bones and liver, as reported by Piney [17].

Our first case (M.F.) corresponds to the general description of Gaucher's disease, the character and distribution of the large cells being typical. The lesions in the spleens of the other cases correspond histologically and micro-chemically to those of the first case. None of the cases showed any evidence of syphilis or tuberculosis, although the latter disease is cited by Schlagenhaufer [5]

and Ewing [18] as being an ætiological factor. Aerobic and anærobic cultures made from the spleens excised at operation remained sterile, and no spirochætes were found on darkground examination or in stained films. In subcutaneous inoculation into guinea-pigs of splenic material and, in the first case, of mesenteric and bronchial glands ground up in saline, no lesions were noted when the animals were killed eight weeks later.

Origin of Gaucher Cells. There has been much variance of opinion regarding the origin of the Gaucher cells, American writers favouring endothelium as well as reticulum, while the German writers are of the opinion that these cells arise from the reticulum only. From our studies we are inclined to agree with the latter view. We have noted transition stages between reticular cells and Gaucher cells in the Malpighian bodies of the spleen and also in the lymphatic glands. Further, in all the organs and tissues where the large cells were met, they always maintained a very close relationship to the reticulum. Mandelbaum [19] noted the close relationship between the Gaucher cells and certain large cells in the lymphatic germ-centre, and he drew the conclusion that these large cells were members of the lymphatic series, and that they gave rise to Gaucher cells. In histological preparations of normal spleens from children as well as of spleens from cases of Gaucher's disease, we have observed in the germ-centres of the Malpighian bodies and lymphatic glands, similar cells, generally more oval than round and occasionally having a very close relationship to reticular fibres but differing in their staining and phagocytic reactions from true lymphatic germ-cells. We have regarded such cells as reticular in origin, and have also observed, as noted above, what appeared to be transition stages between such cells and Gaucher cells. The first case (Fig. 2) supports this view, the germ-centres being entirely replaced by Gaucher cells. Downey's work, quoted by Mandelbaum [7], points to the Gaucher cells taking origin from the reticulum in the lymphatic germ-centres, and also from the reticular structures around lymph follicles. With this view, we are in complete agreement, and in the first case (M.F.), where the lymphatic glands were studied, we have noted changes similar to those quoted by Mandelbaum, namely, thickening of the reticulum and, in places, swelling of the reticular fibres. Another point in favour of the reticular origin of such cells is the appearance in staining of the cells by potassium ferrocyanide and hydrochloric acid, the Gaucher cells either showing no iron reaction or a very slight diffuse reaction, whereas in the endothelial cells, a granular reaction is obtained. Pick [12] has also commented on this point.

Lipoid Content of Gaucher Cells. One of the most characteristic features of the Gaucher cells is their reticulated appearance, due to a lipoid-like substance which they contain. Regarding the nature of this substance, much controversy has arisen, and Mandelbaum [7] who has written extensively on the question has always been emphatic that the cells do not give the micro-chemical reaction for lipoids, although he states that the organs which are affected have a high lipoid content (lecithin and cholesterin in combination with protein of a complex nature). Similar results have been reported by Epstein [20] who isolated a crystallising cerebroside which he identified as kerasin, and in

addition, found phosphatides present, though he failed to find either lecithin or cholesterin. Bloom [21] also found that the cells when stained with Sudan III and hæmatoxylin gave a slight greyish-yellow tinting of the protoplasm, although he decides against the cells containing lipoids. In our cases, we have found that while the reaction to lipoid stains is not typical of the lipoids met with in ordinary histological work, still it appeared as if the cells did take up some of the lipoid stain as noted by Bloom. On further experiments, we found that by heating frozen sections to 100° C. in water or glycerine and then staining with Sudan III or Nile Blue, the cells took up the fat stain to a slight degree, and anisotropic bodies were seen in the cells. This fact has not been previously noted and would appear to be due to a hydrolysis caused by the heating, or what is more probable, a melting and running together into large globules of the lipoid substances which are present in the cells in a diffuse phase. Further studies of these large cells will be published at a later date. In the meantime, however, it is our opinion that the Gaucher cells do contain a substance of a fatty nature and we suggest that the disease is a reaction of the cells of the reticulo-endothelial system to some metabolic error in lipoid metabolism.

Although it is generally believed that the large cells are pathognomonic of Gaucher's disease, it must be remembered that somewhat similar cells do occur in other conditions and on several occasions have been confused with Gaucher cells. For example, in diabetes with lipæmia, lipoid substances may be stored in the reticulo-endothelial cells of the spleen and in some cases there is such a proliferation of the cells that splenomegaly results. These cells may readily be confused with Gaucher cells. Moreover, after feeding animals with cholesterol over a long period of time, numerous large cells containing doubly refractile lipoids appear in the spleen, liver and lymph-glands. The similarity of these cells to those seen in Gaucher's disease is so marked that Aschoff [22] called the condition "pseudo-Gaucher." In Niemann's disease [23] cells which give the usual reactions for lipoids are found throughout many organs including the suprarenals while the liver in this condition shows no evidence of cirrhosis. As already mentioned, the material present in the large cells in Gaucher's disease is probably of a complex lipoid nature, and it would seem that the cells of the reticulo-endothelial system store these substances in much the same way as, in vital staining of animals, the injected dye is picked out from the blood and stored by such cells. In the diseased condition, however, the storage capacity becomes overtaxed and there results a great proliferation of cells of reticulo-endothelial origin. If such a view is correct, it brings the histological lesions met with in diabetes with lipæmia, in the experimentally produced cholesterolæmia, in Niemann's disease and in Gaucher's disease, all into the same category, *i.e.*, a reaction on the part of the reticular cells to some abnormal product of lipoid metabolism, the difference in the various diseases depending for the most part on the nature of the lipoid substances concerned. The cirrhosis of the liver would appear to be due to necrosis occurring in masses of Gaucher cells, and also to the laying down of collagen in a hypertrophic reticulum.

Conclusions.

1. Five cases of Gaucher's disease are reported and the clinical and pathological features discussed.

2. The diagnosis of Gaucher's disease can be readily confirmed by the histological examination of splenic tissue obtained by splenic puncture. The procedure adopted is described.

3. The disease is probably a reaction on the part of the reticulo-endothelial system to some abnormal or unwanted product of lipoid metabolism.

4. Gaucher's disease, Niemann's disease, changes observed in experimentally produced cholesterolæmia and in diabetes with lipæmia, fall, we believe, into the same category, depending on the nature of the lipoids involved.

Splenectomy was performed in these cases by Mr. Alex. MacLennan, Visiting Surgeon, Royal Hospital for Sick Children, Glasgow, to whom we are indebted for permission to make use of his reports. We have also much pleasure in acknowledging the grateful help and advice of Prof. Robert Muir and Prof. Leonard Findlay.

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A STUDY OF PHOSPHORUS ABSORPTION IN NORMAL AND RACHITIC CHILDREN.

BY

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The disordered metabolism of the inorganic constituents of bone in the rachitic child has long been the subject of research, in the course of which a mass of valuable experimental data has accumulated. Nevertheless, it must be admitted that in rickets the *causa causans* remains obscure, and further, that with regard to the interpretation of much of the experimental evidence in our possession, there is no unanimity of opinion. Thus, it is still an undecided point whether the fundamental error lies in the assimilation of phosphorus or in that of calcium, the issue being confused by the intimate reciprocal relation which exists between these elements in every phase of their metabolism.

One of the most constant findings in rickets is a reduction in the inorganic phosphorus content of the blood, a point first noted by Iversen and Lenstrup (1) and shortly afterwards confirmed by Howland and Kramer (2). On the other hand, the blood calcium, at least in uncomplicated rickets in the human subject, is not far removed from the normal (3). A consideration of these facts, together with the results of metabolism experiments on rachitic as compared with normal children, led Howland (4) to conclude that the essential defect in rickets consists in an impaired absorption of phosphorus. Other American investigators, notably Hess and his collaborators (5) (6) have laid similar stress on the question of phosphorus metabolism in relation to rickets.

These views are not, however, shared by the Glasgow School. In 1924 Findlay (7) stated that in his judgement the intrinsic disturbance was one of calcium metabolism, and while admitting that the possibility of a defective fixation of calcium by the growing cartilage had not definitely been excluded, he was inclined to the idea that the failure of calcification in rickets is the result of interference with the normal absorption of lime salts from the gut. The experimental studies of Telfer (8) on normal and rachitic infants led him also to the conclusion that in the latter the role of defective calcium assimilation was of the first importance.

A survey of the facts, so far as they are at present known, with regard to calcium and phosphorus metabolism in health and in rickets, will serve to indicate the grounds upon which these divergent opinions are based.

In most foodstuffs calcium and phosphorus occur chiefly in inorganic form, though also to a lesser extent in organic combination. It is in the

former that they are for the most part absorbed. Solution of the greater part of the compounds ingested is brought about by the acid gastric juice, and absorption then proceeds until, passing into the intestine, the chyme becomes alkalinized, and the calcium remaining unabsorbed is thrown out in the form of the insoluble tertiary phosphate of lime. Further free absorption cannot then take place. Apparently, therefore, even under normal conditions, absorption of calcium is limited to a fraction of the intake, and occurs, for the most part, over a very restricted area. Moreover, it is largely influenced by the *p*H of the secretions in this area, and may be seriously interfered with by any increase in the latter. Telfer's work [8] on the normal metabolism of calcium in children and in animals goes far to confute the theory, long held, that calcium is absorbed in excess of requirements and to a large extent re-excreted into the intestine. On the contrary, it points definitely to the fact that " the greater part of the calcium intake is restricted to the gut, and except the small amount excreted in the urine, the amount absorbed is nearly equivalent to the amount retained." The same experimental study showed the significance of the urinary calcium as an approximate measure of the absorption of this substance. Increase in the calcium intake was followed by improved retention accompanied by a slight rise in the urinary calcium, while a diminished intake resulted in a corresponding fall. Ahlquist's investigations [9] of the metabolism of lime in normal children also demonstrated the importance of this point.

In contrast to calcium, phosphorus is freely absorbed from the alimentary tract. Its inorganic salts are dissolved by the gastric juice, and the bulk of the ingested phosphorus is probably absorbed in this form [8]. During intestinal digestion organic phosphorus compounds are split up, and the phosphoric acid thus set free is further rendered available for absorption.

Normally, phosphorus is found in considerable quantity in both urine and fæces. The fæcal phosphorus has been shown to be simply the unabsorbable mineral residue of the food. Locked up in insoluble combination with calcium, it has passed through the body without taking any part in metabolism beyond the intestinal wall. Excess of phosphorus over the amount required for the conversion of calcium in the intestine into $Ca_3(PO_4)_2$ is absorbed, and in so far as it is not required for growth and repair of tissue, is eliminated in the urine.

Under normal conditions, the percentage of phosphorus absorbed depends mainly upon the extent to which precipitation of $Ca_3(PO_4)_2$ takes place. Any factor, for example, excess of lime in the food, which leads to increased formation of this salt, will restrict a larger amount of phosphorus to the intestine, leaving relatively less to be excreted by the kidneys, while the opposite effect will be produced by factors causing a reduced formation of $Ca_3(PO_4)_2$. Thus it has been shown by Hoobler [10] and confirmed by Telfer [8] that an excess of fatty derivatives in the intestine results in the elimination of increased quantities of calcium in the form of insoluble soaps, so that relatively less phosphorus is calcium-bound, and more is free to be absorbed.

These facts have an important bearing upon the deranged metabolism of the elements in question in rickets. In the active stage of this disease, as the early experiments of Schabad (11) proved, and those of other observers have since confirmed, there is a greatly diminished retention of calcium and phosphorus, more especially of the latter, and abnormally large quantities of both are excreted in the fæces. In the urine calcium is reduced to an insignificant fraction, while the amount of phosphorus, though little changed absolutely, constitutes a much smaller proportion of the total excretion than in health. On the other hand, the healing stage of rickets is characterized by an abnormally high positive calcium-phosphorus balance, and a reduction in the elimination of these by way of the intestine. The quantity of phosphorus in the urine remains practically the same, so that the improved retention occurs at the expense of that which had previously been excreted in the fæces. The change in the partition of calcium between urine and fæces is less striking, but Orr and others (12) demonstrated that in a number of cases an increased percentage was excreted in the urine, and that this was due quite as much to actual increase in the quantity of calcium found in the urine, as to the diminution of this element in the fæces. Wills, Sanderson and Paterson (13) have also recorded an increase in the urinary calcium during the healing stage of rickets.

If Telfer's hypothesis be accepted, that under normal physiological conditions the calcium content of the fæces represents not an excretion from the blood, but merely the unabsorbed portion of the intake, then the importance of its application in the case of rickets becomes manifest. In the absence of proof that in this disease an abnormal mode of excretion exists (and as Findlay (7) has pointed out, indisputable evidence to this effect is lacking) it follows that the surplus of calcium in the fæces in rickets is the result, not as had been generally assumed, of increased excretion into, but of diminished absorption of lime from the gut. The influence of an excess of calcium upon the absorption of phosphorus is well known, and has already been mentioned. Whether such an excess be due to increased intake, or to defective absorption of calcium, the effect will equally be to restrict an increased amount of phosphorus to the intestine. It follows that the abnormal excretion of phosphorus in the fæces in rickets may be entirely secondary to the error in calcium metabolism, and is not necessarily to be taken as evidence of an impaired power of absorbing phosphorus as such.

The results of certain metabolism experiments carried out by Findlay and Telfer (7) lend strong support to this view. In two cases of late rickets the diet was adjusted so that it contained a minimal quantity (0·16 grm.) of CaO per day, and the excretion of calcium and phosphorus was followed. It was found that of the total amount of phosphorus eliminated, 74 per cent. occurred in the urine. Increase in the daily intake of CaO by the addition of calcium lactate to the diet brought about a striking change, in that the urinary phosphorus was much reduced, in one case to almost half the previous amount. It was thus shown that in these cases absorption of phosphorus was actually unimpaired, though the fact emerged clearly only when the deterrent influence

of calcium was as far as possible removed, a point to which attention was directed for the first time.

In view of these observations it became important to determine whether the concentration of phosphorus in the serum is influenced in like manner by variations in the calcium and phosphorus intake, and in particular, whether any significant difference can be demonstrated between such response in the rachitic and the normal child. It was with this object in view that the present investigation was undertaken.

The work was divided into two parts. In the first, the level of the inorganic phosphorus of the serum in normal and rachitic children was followed throughout a period of several weeks, during which alterations were made from time to time in the intake of calcium and phosphorus. In the second, the absorption of phosphorus in rickets was compared with that in health by tracing the rise in the serum phosphate in both, following the administration by mouth of a single dose of acid sodium phosphate.

Part I. Study of Serum Phosphorus.

Method.

The first group selected for study consisted of three children, from $1\frac{1}{4}$ to $1\frac{2}{3}$ years of age who suffered from rickets in the active stage as evidenced by radiograms; the second, of nine non-rachitic children varying in age from 5 months to 10 years. Of the latter, hereinafter briefly designated "normal," one had recovered from chorea, two from bronchitis, and the remainder suffered from chronic rheumatic carditis, conditions presumably unaccompanied by any error in calcium or phosphorus metabolism.

A basic diet low in calcium was chosen. The older children (8-10 years) received the following daily allowance:—

Diet A. Meat 100 grm., potato 120 grm., bread 200 grm., banana 50 grm., butter and honey of each 25 grm., orange juice 50 c.c., and cocoa 6 grm. This contains, according to a calculation from tables supplied by Sherman [14], approximately 0·16 grm. CaO, and 1·16 grm. P_2O_5. It was impossible to reduce the calcium intake to a comparable extent in the case of the younger children (under 2 years) whose diet necessarily contained a considerable quantity of milk. Two of these received daily 0·79 grm. CaO and 1·1 grm. P_2O_5 in the following diet:—

Diet B. Milk, 450 c.c. diluted with water 600 c.c., 40 per cent. cream 30 c.c., sugar 62 grm., bread 30 grm., and butter 4 grm. In the remaining two cases, a normal child of 5 months, and a rachitic of $1\frac{1}{2}$ years, the diet consisted of whole milk, no attempt being made to reduce the calcium intake.

Changes in the intake of CaO and P_2O_5 were effected by the addition of different amounts of calcium lactate and acid sodium phosphate to the diet, and in the majority of cases were so arranged that during the earlier stages of the experiments there was a gradual increase in the daily intake of phosphorus, while that of calcium remained low; in the final stage the calcium intake was at one step largely augmented, the phosphorus being maintained at its previous level. These alterations in the diet were made at intervals of five or six days, and during each period the serum phosphate was twice

determined, usually on the third and fifth or sixth days. Throughout the experiments all the patients were confined to bed.

The method employed for estimation of the inorganic phosphorus of the serum was that of Tisdall [15]; and due care was taken in every case to separate the serum from the blood as rapidly as possible.

Results.

In the later experiments minor changes were made in the amounts of calcium and phosphorus salts added to the diet, hence it has been necessary to divide the results into groups. Those obtained in the normal cases are summarised in Tables I.-IV., and graphed in Charts I.-V., those in the rachitic cases in Tables V. and VI., and Charts VI. and VII.

TABLE I.

NORMAL CHILDREN.

Day of Experiment.	Diet.	Intake.		P. in mg. per 100 c.c. serum.	
		CaO	P_2O_5	Case 1.	Case 2.
1—4	Diet (A) + Ca. lact. 5 grm.	1·44	1·15	4·2	4·4
4—7	„ „	0·16	1·15	4·1	4·2
7—9	„ „	0·16	1·15	4·0	4·2
9—12	„ „ + NaH_2PO_4 3 grm.	0·16	2·92	4·4	5·4
12—14	„ „ + NaH_2PO_4 3 grm.	0·16	2·92	4·3	5·2
14—17	„ „ + NaH_2PO_4 6 grm.	0·16	4·69	4·4	5·6
17—19	„ „ + NaH_2PO_4 6 grm.	0·16	4·69	5·0	5·8
19—22	„ „ + NaH_2PO_4 6 grm. and Ca. lact. 5 grm.	1·44	4·69	5·1	5·4
22—24	„ „ + NaH_2PO_4 6 grm. and Ca. Lact. 5 grm.	1·44	4·69	5·0	5·9
24—27	„ „ + NaH_2PO_4 6 grm. and Ca. lact. 12·5 grm.	3·35	4·69	4·9	—
27—30	„ „ + NaH_2PO_4 6 grm. and Ca. lact. 12·5 grm.	3·35	4·69	4·7	—

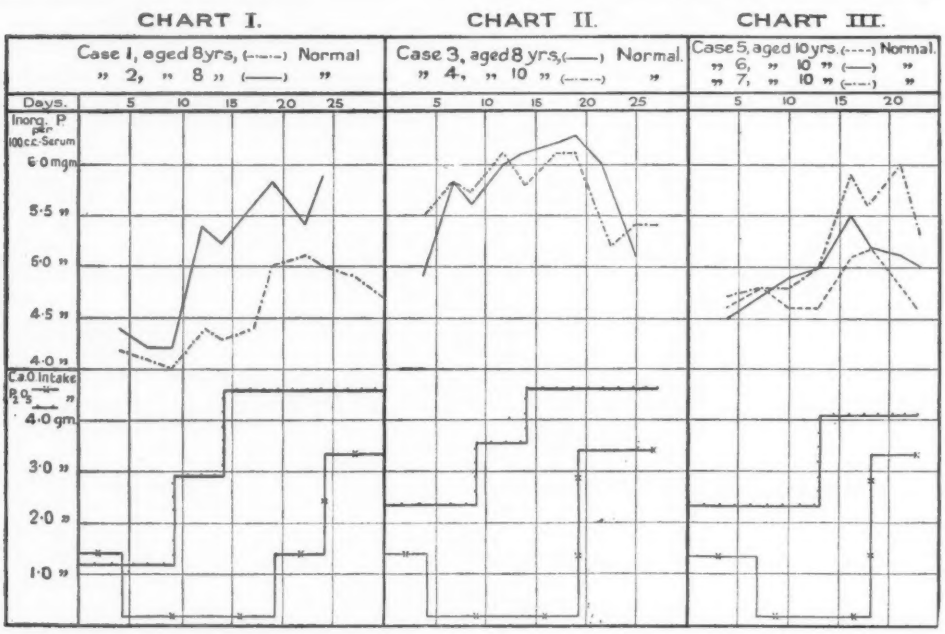
CASES 1 and 2. (Table I.) (Chart I.)

In both cases the serum phosphorus was unaffected by the initial reduction of calcium in the diet, but showed a definite rise in response to increase in the intake of phosphates. This was more marked in Case 2, in which it amounted to 1·4 mg. per 100 c.c. Subsequent slight increase in the calcium intake was without effect on the serum phosphorus, and at this point the investigation in Case 2 was unavoidably cut short. In Case 1 a further increase in the calcium was followed by a slight but definite fall in the serum phosphorus, which, however, still remained well above the original level. It is to be noted that the CaO : P_2O_5 ratio at the beginning of this experiment was nearly twice as great as at the end.

TABLE II.

Normal Children.

Day of Experiment.	Diet.	Intake.		P. in mg. per 100 c.c. serum.	
		CaO	P_2O_5	Case 3.	Case 4.
1—4	Diet (A) + Ca. lact. 5 grm. + NaH_2PO_4 2 grm.	1·44	2·33	4·9	5·5
4—7	„ „ + NaH_2PO_4 2 grm.	0·16	2·33	5·8	5·8
7—9	„ „ + NaH_2PO_4 2 grm.	0·16	2·33	5·6	5·7
9—12	„ „ + NaH_2PO_4 4 grm.	0·16	3·51	6·0	6·1
12—14	„ „ + NaH_2PO_4 4 grm.	0·16	3·51	6·1	5·8
14—17	„ „ + NaH_2PO_4 6 grm.	0·16	4·69	6·2	6·1
17—19	„ „ + NaH_2PO_4 6 grm.	0·16	4·69	6·3	6·1
19—22	„ „ + NaH_2PO_4 6 grm. + Ca. lact. 12·5 grm.	3·35	4·69	6·0	5·2
22—25	„ „ + NaH_2PO_4 6 grm. + Ca. lact. 12.5 grm.	3·35	4·69	5·1	5·4
25—27	„ „ + NaH_2PO_4 6 grm. + Ca. lact. 12·5 grm.	3·35	4·69	—	5·4



Showing Serum P. Curves in Feeding Experiments in Normal Children (Cases I—VII).

Cases 3 and 4. (Table II.) (Chart II.)

In this group the diet was adjusted so that there was no great discrepancy between the CaO : P_2O_5 ratios at the beginning and at the end of the experiment, the figures being 0·6 and 0·7 respectively.

Case 3 responded to an increasing phosphorus intake with a rise of 1·5 mg. P. per 100 c.c serum; later an increase in the calcium of the diet was followed by a marked drop in the serum phosphorus, which almost regained its initial level.

The corresponding changes in Case 4, though more erratic, were similar in general trend.

TABLE III.

Normal Children.

Day of Experiment.	Diet.	Intake.		P. in mg. per 100 c.c. serum.		
		CaO.	P_2O_5.	Case 5.	Case 6.	Case 7.
1—4	Diet (A) + NaH_2PO_4 2 grm. + Ca. lact. 5 grm. ..	1·44	2·33	4·6	4·5	4·7
4—7	„ „ + NaH_2PO_4 2 grm. + Ca. lact. 5 grm. ..	1·44	2·33	4·8	4·7	4·8
7—10	„ „ + NaH_2PO_4 2 grm. ..	0·16	2·33	4·6	4·9	4·8
10—13	„ „ + NaH_2PO_4 2 grm. ..	0·16	2·33	4·6	5·0	5·0
13—16	„ „ + NaH_2PO_4 5 grm. ..	0·16	4·1	5·1	5·5	5·9
16—18	„ „ + NaH_2PO_4 5 grm. ..	0·16	4·1	5·2	5·2	5·6
18—21	„ „ + NaH_2PO_4 5 grm. + Ca. lact. 12·5 grm. ..	3·35	4·1	4·8	5·1	6·0
21—23	„ „ + NaH_2PO_4 5 grm. + Ca. lact. 12·5 grm. ..	3·35	4·1	4·6	5·0	5·3

Cases 5, 6 and 7. (Table III.) (Chart III.)

An effort was made still farther to increase the CaO : P_2O_5 ratio in the final stage of the experiment. As it was impracticable to give more than 12·5 grm. of calcium lactate daily, this object was arrived at by reducing the amount of NaH_2PO_4 added to the diet.

All three cases exhibited a rise in serum phosphorus following increased intake of phosphates, although in Case 5 the increment was small. Again the addition to the diet of calcium in excess was attended by a fall in the serum phosphorus, though not to the original level.

TABLE IV.

Normal Child.

Day of Experiment.	Diet.	Intake.		Serum P.
		CaO.	P_2O_5.	Case 8.
1—4	Milk 825 c.c.	1·4	1·8	4·1
4—7	„ „	1·4	1·8	4·2
7—10	„ „ + NaH_2PO_4 4 grm.	1·4	4·17	5·0
10—13	„ „ „ „	1·4	4·17	4·6
13—16	„ „ „ „	1·4	4·17	4·7
16—20	„ „ „ „ + Ca. lact. 10 grm.	3·9	4·17	4·0
20—22	„ „ „ „ „ „	3·9	4·17	4·2

CASE 8. (Table IV.) (Chart IV.)

The basic diet in this instance was whole milk, and the calcium-phosphorus intake was therefore high at the beginning, and greatly in excess at the end of the experiment. In the last 4 days there was some slight vomiting.

The rise in the serum phosphorus following high phosphorus feeding was definite but not very marked, amounting to 0·8 mg. per 100 c.c. During the last period, when the CaO : P_2O_5 ratio was 0·9, as compared with 0 7 at the outset, a diminution of 0·7 mg. per 100 c.c. occurred in the phosphorus of the serum.

CASE 9. (CHART V.)

In this case the calcium-phosphorus intake remained constant throughout. During the first 5 days the serum phosphorus was determined daily, and for the remainder of the period estimations were made at intervals of 3 or 4 days. The total range was from 4·9 mg. to 5·3 mg. P. per 100 c.c., and for the most part the day to day fluctuations were negligible.

TABLE V.

ACTIVE RICKETS.

Day of Experiment.	Diet.	Intake.		P. in mg. per 100 c.c. serum.	
		CaO.	P_2O_5.	Case 10.	Case 11.
1—3	Milk 1050 c.c.	1·73	2·3	3·6	3·9
3—6	Diet (B) + NaH_2PO_4 1·6 grm.	0·78	2·03	3·7	3·8
6—9	„ + NaH_2PO_4 1·6 grm.	0·78	2·03	3·5	3·9
9—12	„ + NaH_2PO_4 3·3 grm.	0·78	3·03	—	3·9
12—14	„ + NaH_2PO_4 3·3 grm.	0·78	3·03	4·1	4·2
14—17	„ + NaH_2PO_4 4·2 grm.	0·78	3·56	3·4	3·9
17—19	„ + NaH_2PO_4 5 grm.	0·78	4·06	3·5	4·3
19—22	„ + NaH_2PO_4 5 grm. + Ca. lact. 4 grm. ...	1·8	4·06	3·3	3·9
22—24	„ + NaH_2PO_4 5 grm. + Ca. lact. 4 grm. ...	1·8	4·06	—	3·7
24—27	„ + NaH_2PO_4 5 grm. + Ca. lact. 8 grm. ...	2·8	4·06	—	3·7
27—29	„ + NaH_2PO_4 5 grm. + Ca. lact. 8 grm. ...	2·8	4·06	—	3·5

CASES 10 AND 11. (Table V.) (Chart VI.)

In Case 10 the behaviour of the serum phosphorus was somewhat erratic. Unfortunately the experiment had to be curtailed before the final increase in calcium had been made, but even the very moderate increase that was effected, was associated with a slight fall in the serum phosphorus. The changes in the latter that occurred in Case 11 appeared to be more definitely related to the diet. Thus, increased intake of phosphates was followed by a definite rise in the serum phosphorus, while subsequent increase in calcium apparently brought about a fall of 0·8 mg. per 100 c.c. It is noticeable that in both these cases the serum phosphorus was lower at the end of the experiment than it had been originally.

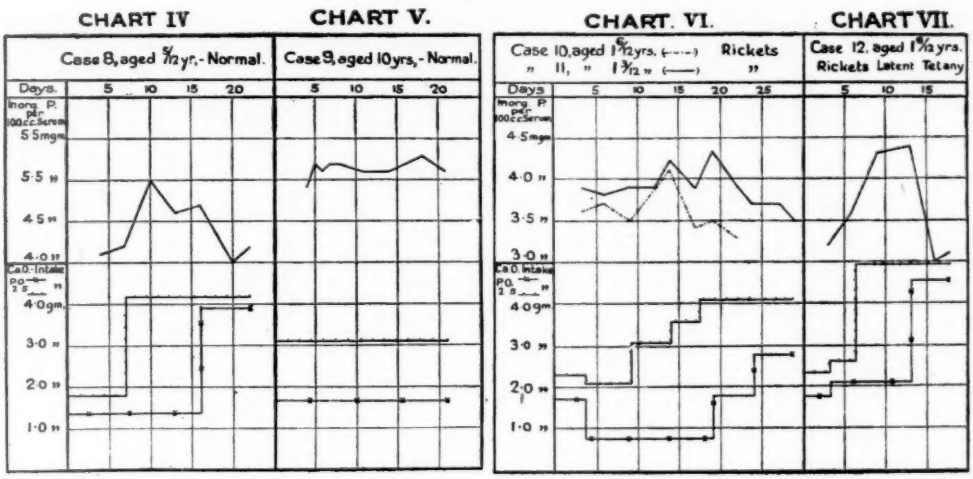


CHART IV
CHART V.
CHART. VI.
CHART VII.
Case 8, aged 5/12 yr. - Normal.
Case 9, aged 10 yrs. - Normal.
Case 10, aged 1 4/12 yrs. Rickets
Case 11, aged 1 3/12 yrs. Rickets
Case 12, aged 1 4/12 yrs. Rickets Latent Tetany
Days
Inorg. P. per 100 c.c. Serum
CaO. Intake
P2O5

Showing Serum P. Curves in Feeding Experiments: IV and V, Normal Children (Cases VIII and IX): VI and VII, Rachitic Children (Cases X—XII).

TABLE VI.

Active Rickets—Latent Tetany.

Day of Experiment.	Diet.	Intake.		P. in mg. per 100 c.c. serum.
		CaO.	P_2O_5	Case 12.
1—3	Milk 1050 c.c.	1·78	2·3	3·2
3—6	„ 1200 c.c.	2·04	2·6	3·6
6—9	„ „ + NaH_2PO_4 4 grm.	2·04	5·0	4·3
9—13	„ „ + NaH_2PO_4 4 grm.	2·04	5·0	4·4
13—16	„ „ + NaH_2PO_4 4 grm. + Ca. lact. 10 grm.	4·6	5·0	3·0
16—18	„ „ + NaH_2PO_4 4 grm. + Ca. lact. 10 grm.	4·6	5·0	3·1

Case 12. (Table VI.) (Chart VII.)

As in Case 8, the basic diet was whole milk, and the variations in the calcium-phosphorus intake were similar in both cases. The serum phosphorus (which, however, was already tending upwards) rose considerably when the phosphates in the diet were increased, but the most striking feature of the case was the pronounced fall in the serum phosphorus (1·3 mg. per 100 c.c.) which took place when the calcium intake was substantially augmented.

A disturbing factor in this instance was the appearance, on the 5th day, of Chvostek's sign. From the 6th day onwards, the sign could not be elicited, and at no time was there any other evidence of latent tetany, facts which will be commented upon later.

Discussion.

In interpreting these results it is necessary to bear in mind certain facts with regard to the phosphorus content of the blood and the variations to which, under normal physiological conditions, it is subject.

In contrast to calcium, which varies only within narrow limits, the blood phosphorus fluctuates rather widely. Howland and Kramer [3] who investigated this factor in a number of healthy children, found the average value to be 5·4 mg. inorganic phosphorus per 100 c.c. serum, with 7·1 mg. and 4 mg. per 100 c.c. as the extreme values. The much lower level of phosphate in the serum of adults (averaging, according to Howland and Kramer, 2·1 mg. per 100 c.c.) is attained not by any slow gradations, but by an abrupt fall about the 20th year, which marks the end of the period of active bone growth [16]. The bearing of this fact upon the present investigation is that comparison of figures obtained in the normal and rachitic groups would appear valid, though the average age of the former considerably exceeded that of the latter.

It is stated by Greenwald [17] that the inorganic phosphorus of the serum is increased after food. Experimenting on adults, he found a rise averaging 2·5 mg. per 100 c.c. in the acid-soluble phosphorus of the serum two and a half hours after a meal containing meat, and concluded that "from the large variations found, the content of this form of phosphorus in the serum may be largely dependent on the character of the food and the stage of digestion."

Again, Havard and Reay [18] have recently adduced evidence to prove that muscular activity has an effect upon the phosphorus content of the serum. They found that in adults vigorous exercise produced a rise averaging 10 per cent., followed by a fall of about twice that extent, results which they attributed to changes in the lactacidogen content of the muscles.

Lastly, since the phosphates of the serum are generally held to constitute one of the factors by which the acid-base equilibrium is regulated, their amount might be expected to vary on this count alone. In this connection it is, however, interesting to note that several observers including Denis and Minot [19] and Jones and Nye [20] were unable to establish any relationship between the alkali reserve and the phosphate content of the blood.

In any event it is clear that the term "normal serum phosphorus" is an elastic one, the figure varying not only from one individual to another, but in the same individual from time to time. The questions therefore arise—How far may the variations recorded in the present series of cases be attributed to changes in the calcium-phosphorus content of the diet, and how far are they the result of other factors? It was to decide this point that the experiment on Case 9 was carried out, the results of which are recorded in Chart V. These appear to warrant the conclusion that under controlled conditions of rest and uniformity of diet, the inorganic phosphorus of blood sampled at a regular hour, varies comparatively little from day to day in the normal child. Considering then at present only the normal cases, it may reasonably be claimed that the larger variations recorded are the direct result of changes in the calcium-phosphorus content of the diet. This assumption is supported by the regular trend of the figures themselves, which show that an increased intake of phosphorus consistently gave rise to an increase in the inorganic phosphate of the serum, and that a decline in the level of the latter resulted in every case from the addition of calcium in excess to the diet.

The serum phosphorus does not appear to be influenced with equal readiness in all cases. The fall consequent upon an increased intake of calcium, though definite in every instance, was most marked in Case 3, where it amounted to 1·2 mg. per 100 c.c. serum. In the same child, a rise of 1 mg. per 100 c.c. followed the initial reduction in the calcium intake, though no increase had been made in that of phosphorus. In no case was the serum phosphorus raised definitely above, or depressed below, normal limits.

Experiments upon animals have been recorded by Kramer and Howland [21] and by Park, Guy and Powers [22] in which was studied the influence of changes in the $CaO : P_2O_3$ ratio of the food on the serum phosphate, but the fact that gross departures from the normal were made in the diet, so that in most cases the animals developed rickets, invalidates comparison with the results of the present investigation. Reference may, however, be made to certain experiments on heifers described by Meigs, Blatherwick and Cary [23] from which it appeared that the addition of a calcium salt (in this case $CaCl_2$) to the standard ration resulted in a reduction in the inorganic phosphorus of the plasma. This is in agreement with the results obtained by the writer in the case of normal children, which show that the amount of calcium ingested undoubtedly influences the phosphorus content of the serum.

Certain differences are to be observed between the curves obtained in the normal and in the rachitic groups. In two cases of rickets (Nos. 10 and 11) and particularly in the former, the rise induced in the serum phosphorus during the earlier stage of the experiments was somewhat spasmodic and ill-sustained. The influence of an increased intake of calcium in depressing the serum phosphorus level was, however, very definite, and it is to be noted that in both instances this level was lower at the end of the experiment than it had been at the beginning. Unfortunately no information is available as to the possible extent of the ordinary daily fluctuations in the serum phosphorus in rickets, since it was not found possible, during the period of study, to investigate this point separately in a rachitic infant as had been done in a normal child (Case 9).

Case 12 must be considered separately, as on the third day the experiment was unexpectedly complicated by the development of the facial phenomenon. No other signs of latent tetany could be elicited, and on the fifth and subsequent days, the sign was negative, though a further rise in the serum phosphorus followed the addition of NaH_2PO_4 to the diet. If the case be considered one of latent tetany, the doubt arises whether the striking drop in the serum phosphorus consequent upon the increase in the calcium intake may not have been simply the result of the therapeutic influence of calcium lactate, causing a reversion from the blood picture of tetany to that of uncomplicated rickets. Two considerations seem to negative this possibility. In the first place, there had been no evidence of tetany for several days before the calcium lactate was given; secondly, Anderson and Graham [24] in a study of the ætiology of tetany made the observation that there was no relation between the phosphorus content of the serum and the appearance or disappearance of the tetany.

In this case, therefore, as in the others, the most probable explanation of the effect of a calcium-rich diet upon the serum phosphorus is to be found in the well-recognised fact that an excess of lime in the intestine interferes with the absorption of phosphates by precipitating the latter in insoluble form. Comparison between Cases 7 (normal) and 12 (rachitic) which received practically the same diet, shows that the influence of calcium upon the serum-phosphorus level was much more marked in the latter than in the former, a difference which can best be accounted for by the presumption that in the rachitic child, owing to defective absorption of calcium, there was a relative as well as an absolute excess of this substance in the gut.

PART II.—Study of Phosphorus Absorption.

In the work that remains to be described, the absorption of phosphorus in health and in rickets was investigated by a method which promised to afford direct information on the subject. It has been shown by Klercker and Odin [25] in a study of the genesis of so-called "phosphate tetany," that the introduction by mouth of a soluble phosphate results in a rise in the inorganic phosphorus of the serum. If in rickets there exists any intrinsic defect in the mechanism of phosphorus absorption, one would expect the response of the serum phosphorus to such a dose to be feeble or delayed, as contrasted with that in health.

It was accordingly decided to compare the changes in the phosphorus content of the serum in normal and rachitic children, following the ingestion of NaH_2PO_4.

Method.

In order to obtain a tentative idea of the general form of curve to be expected, a preliminary experiment was carried out upon the writer. Four hours after a meal, blood with withdrawn and 6 grm. NaH_2PO_4 dissolved in 120 c.c. water was then taken; afterwards blood was collected half-hourly for two hours. The inorganic phosphorus per 100 c.c. serum in the various samples was found to be as follows:—(1) 3·8 mg.; (2) 5·4 mg.; (3) 5·5 mg.; (4) 6·2 mg.; (5) 6·1 mg. From the information thus obtained, it was decided to determine the serum phosphorus concentration in all cases immediately before, and at intervals of one, two and four hours after the ingestion of NaH_2PO_4. In preference to regulating the dosage by the body-weight of the patient, the same amount (4 grm. dissolved in 60 c.c. water,) was given in every case. An interval of at least 3 hours was allowed to elapse between the last meal and the beginning of the experiment, and fasting was continued till the last sample of blood had been withdrawn. In all, eleven cases were thus tested, of whom five were normal, four suffered from florid rickets, and two from rickets in the healing stage. As in the earlier experiments the normal controls were convalescent children who had been admitted to hospital some time previously; two cases with rheumatic carditis, two with bronchitis, and one with ileo-colitis. In the cases of rickets the diagnosis was invariably verified by X-ray examination.

Results.

The results obtained in the three groups are collected in Tables VII-IX, and in Charts VIII-X they are presented in graphic form.

TABLE VII.

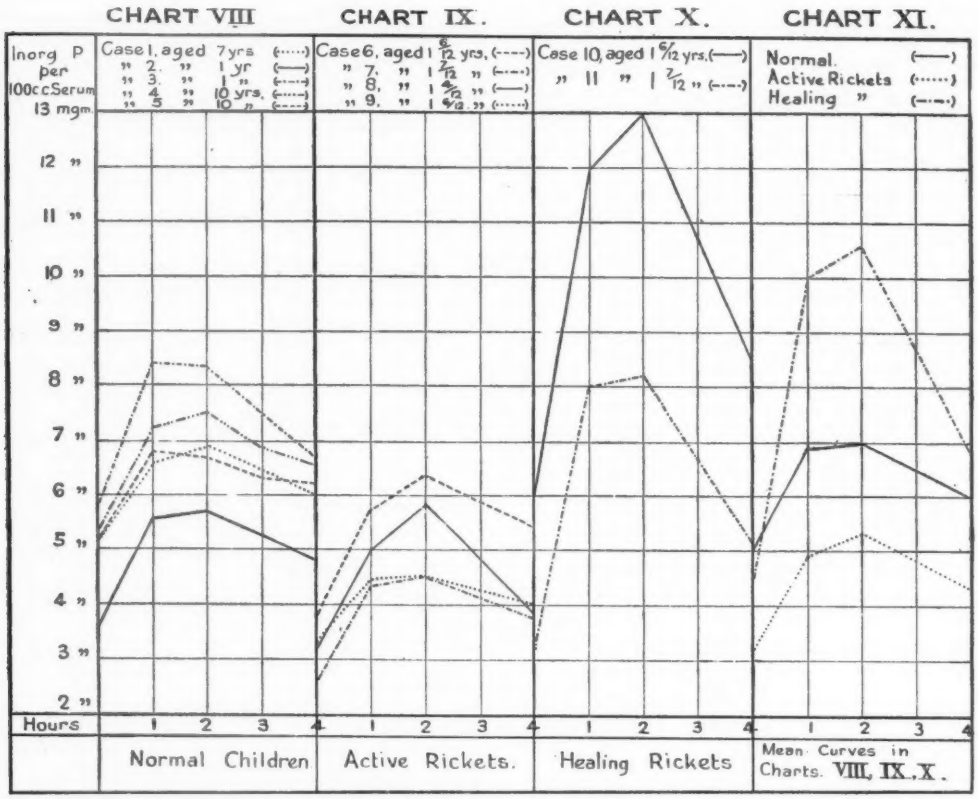
Normal Children.		Case 1. Age 7 years. Wt. 18·2 Kg.	Case 2. Age 1 year. Wt. 6·5 Kg.	Case 3. Age 1 year. Wt. 9 Kg.	Case 4. Age 10 years. Wt. 24 Kg.	Case 5. Age 10 years. Wt. 31 Kg.	Mean.
P. in mg. per 100 c.c. serum.	Before NaH_2PO_4	5·2	3·7	5·8	5·3	5·2	5·0
	1 hr. after 4 grm. NaH_2PO_4	6·6	5·6	8·4	7·2	6·8	6·9
	2 hrs. after 4 grm. NaH_2PO_4	6·9	5·7	8·3	7·5	6·7	7·0
	3 hrs. after 4 grm. NaH_2PO_4	—	—	—	6·9	6·3	6·6
	4 hrs. after 4 grm. NaH_2PO_4	6·0	4·8	6·7	6·6	6·2	6·0
	Max. Increase	1·7	2·0	2·6	2·2	1·6	2·0

TABLE VIII.

Active Rickets.		Case 6. Age $1\frac{7}{12}$ years. Wt. 8·8 Kg.	Case 7. Age $1\frac{1}{2}$ years. Wt. 8·1 Kg.	Case 8. Age $1\frac{1}{3}$ years. Wt. 8 Kg.	Case 9. Age $1\frac{1}{2}$ years. Wt. 8 Kg.	Mean.
P. in mg. per 100 c.c. serum.	Before NaH_2PO_4	3·8	2·6	3·2	3·3	3·2
	1 hr. after 4 grm. NaH_2PO_4 ..	5·7	4·3	5·0	4·4	4·9
	2 hrs. after 4 grm. NaH_2PO_4 ..	6·3	4·5	5·8	4·5	5·3
	4 hrs. after 4 grm.	5·4	3·8	3·9	4·0	4·3
	Max. Increase	2·5	1·9	2·6	1·2	2·1

TABLE IX.

Healing Rickets.		Case 10. Age $1\frac{1}{2}$. Wt. 9·1 Kg.	Case 11. Age $1\frac{7}{12}$. Wt. 8·4 Kg.	Mean.
P. in mg. 100 c.c. serum.	Before NaH_2PO_4	6·0	3·1	4·5
	1 hr. after 4 grm. NaH_2PO_4 ..	12·0	8·0	10·0
	2 hrs. after 4 grm. NaH_2PO_4.. ..	13·0	8·2	10·6
	4 hrs. after 4 grm. NaH_2PO_4.. ..	8·5	5·2	6·8
	Max. Increase	7·0	5·1	6·1



Showing Serum P. Curve after Administration per os of 4 grm. NaH_2PO_4 (Cases I—XI).

From Chart VIII it will be observed that the test yielded in every case a curve of well defined form, with a steep rise during the first hour and a gradual decline during the third and fourth hours. The average increase recorded was 2 mg. P. per 100 c.c., or 40 per cent. Case 2 calls for special comment on account of the unusually low initial level of the serum phosphate. This child presented no clinical signs of rickets but the result of serum analysis suggested that an X-ray examination of the wrist should be made. This showed, however, a completely normal condition of the bones. The existence of a subnormal phosphorus content of the blood in the absence of rickets has previously been recorded. Anderson [3] who determined the blood phosphorus in a large series of normal and rachitic children, found a low value in a number of cases which failed to develop rickets during a period of observation; in no case did a low value indicate the presence of rickets before other signs of the disease had been recognised. On these grounds it was considered justifiable to include Case 2 in the normal series.

If the curves in the normal cases are now compared with those obtained in active rickets, it will be seen that no significant difference exists between them. The general form of the curves in rickets is the same, the peak occurs at the end of two hours, and the average increase is 2 mg. P. per 100 c.c. serum. In only one instance, namely in Case 9, was the rise in the serum phosphorus (1·2 mg. per 100 c.c.) less than in any of the normal cases. Against this may

be set the fact that in Case 8, which presented clinical and radiographic signs of the most severe rickets, an increase of 2·5 mg. P. per 100 c.c. serum was induced, which compares very favourably with the average of 2 mg. per 100 c.c. in the normal group. Briefly, it may be said that in these cases of rickets the serum-phosphorus curve, except that it was transposed to a lower level, differed very little from that of healthy children.

Strikingly different results were yielded by the cases of healing rickets. One of these (Case 10) had been under treatment in hospital for some time, and showed every sign, clinical and radiographic, of rapid healing; the other (Case 11), showed a mild degree of rickets, and here also, X-ray examination showed that recovery was taking place. In both cases administration of 4 grm. of NaH_2PO_4 produced within an hour an enormous increment in the serum phosphorus, which in another hour had still further slightly increased. Thereafter, a sharp decline in the curve showed that the excess was being rapidly removed from the blood. Of the two cases, No. 10, in which healing was further advanced, exhibited the greater rise, amounting to 7 mg. per 100 c.c. serum.

In Chart XI the mean curves in the three groups have been assembled for easy comparison, and the fact that by far the greatest rise was found in healing rickets is clearly brought out.

In the foregoing the validity of comparing results in children of widely differing weights may be questioned, since all received the same dose of NaH_2PO_4, but it should be noted that in the normal children there was no apparent relation between the body-weight and the extent of the increase in the serum phosphorus, as reference to Table VII will show. Thus in Case 4, with a weight of 24 kg. there was recorded a rise of 2·2 mg. per 100 c.c., while in Case 2 weighing only 6·5 kg. the corresponding figure was 2 mg. per 100 c.c. It is probable that in tests of this kind with soluble phosphates as in those with glucose [26], regulation of dosage by weight is of doubtful importance, since increase beyond a certain point in the amount ingested does not lead to a proportionate increase of the substance concerned in the blood.

Reference has been made to the fact that the children on whom these experiments were carried out had in every case fasted for at least 3 hours previously. This condition was observed in order that the absorption of the phosphorus itself might be tested, influenced as little as possible by the presence of any unabsorbed calcium in the stomach or upper part of the intestine.

As has been pointed out elsewhere, conclusions regarding internal metabolism which are based upon the results of analysis of the peripheral blood must be accepted with a certain degree of reserve, influenced as they necessarily are by multiple and often incalculable factors. Thus in the experiments described, the changes in the concentration of phosphorus in the serum depended not only upon the rate of absorption from the gut but also upon the rapidity with which the excess phosphate was removed from the blood by the tissues, and in particular by the kidneys: but in the absence of evidence of any abnormality in the rate of excretion of phosphates, it is perhaps not unreasonable

to regard the extent of the increase in the serum phosphorus following the ingestion of NaH_2PO_4, as an approximate measure of the absorption of that substance. If this be conceded, the foregoing experiments may be said to show (1) that in active rickets there is not necessarily any defect in the absorption of phosphorus, since in four cases studied the latter was found to be, on the average, equal to that in healthy children; (2) that in healing rickets the absorption of phosphorus may be three times as great as in health.

The latter observation is in accordance with the results of metabolism experiments recorded by Schabad [11], and other observers [8a] which show that the healing stage of rickets is characterized by an abnormally high balance of calcium and phosphorus, sometimes 60 per cent. to 80 per cent. of the quantity ingested being retained, or roughly twice the normal amount.

Summary.

In a study of the inorganic phosphorus of the serum, and the manner of its response to variations in the calcium-phosphorus intake, in eight normal and three rachitic children, the following observations were made.

A diet poor in calcium, and rich in phosphorus gave rise to an increase, though not beyond normal limits, in the phosphorus content of the serum.

Subsequent addition of calcium in excess to the diet induced a fall in the serum phosphorus, an effect which, while definite in every case, was more marked in the rachitic than in the normal children.

It was thus shown that in the cases in question the serum phosphorus was undoubtedly influenced by the amount of the calcium intake, excess of the latter being equivalent in effect to a diminished supply of phosphorus. The fact that the effect of calcium excess was greater in the rachitic children may be explained in the light of the hypothesis that in rickets, owing to defective absorption of calcium, the normal deterrent action of this element on phosphorus absorption is intensified.

The phosphorus absorptive power, as indicated by the rise in the inorganic phosphorus of the serum following the ingestion of 4 grm. of NaH_2PO_4, was separately investigated in 11 children of whom 5 were normal, 4 suffered from active rickets and 2 showed healing rickets.

It was found that in the cases of active rickets the average absorption was the same as in the healthy children, while in those of healing rickets it was abnormally high.

From a few examples, however apparently convincing, it is impossible to gather any general conclusion, but interest attaches to the foregoing results in that they are in keeping with the hypothesis of defective calcium absorption in rickets, while with the view that phosphorus metabolism is primarily at fault, they are directly at variance.

The work described in the preceding pages was carried out in the Royal Hospital for Sick Children, Glasgow, and was undertaken at the suggestion of Professor Leonard Findlay, for whose encouragement and valuable help the writer is deeply grateful.

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THE FUNCTION OF BREAST FEEDING

BY

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The cases reported in this paper were breast-fed babies attending various Infant Centres in Croydon. The observations cover a period of six years and are limited to infants attending from the first or second month of life, totally breast fed without supplementary feeds of any sort for eight or nine months, and still under observation at the end of their first year. A larger number of cases first attending later than the second month or receiving part supplementary feeds before the age of eight months or discontinuing attendance before the end of the first year has not been included, although these were managed on similar lines and provided data similar to those recorded.

The cases are arranged in two groups :—

(*a*) A series of 103 cases fed on four feeds a day from early infancy, frequently from one month onwards, never later than from the sixth month ; illustrated by a chart (Chart I) giving the average weights at birth, six months, eight months and one year.

(*b*) A series of ten cases restricted to a total of three feeds per day, as a rule for reasons connected with the mother's health and her ability to continue nursing. Of these, weight-charts (Charts II-V) and individual histories are presented.

The Lactatory Zone of Efficiency.

The basis of the observations was an enquiry into the functional efficiency of lactation and its action under reduced stimulation, on the hypothesis that a lactatory " zone of efficiency " might exist as in the case of other physiological functions. A few words of explanation may be advisable. We accept in talking of liver and kidney the idea of such a zone when we describe " thresholds" beyond which in the absence of organic defect certain symptoms may appear, due to purely functional irregularity, insufficiency or overstrain. In the normal person the amount of work performed daily by these organs will vary considerably, but will not ordinarily pass the limits of that " zone" within which response will go hand in hand with stimulation. In considering another example we know that a digestive apparatus which for one reason or another has continuously been working under diminished pressure due to diminished intake of food, will show a functional inefficiency to cope suddenly with an intake restored to normal level : and that, contrariwise, the function, if consistently overworked and overstimulated, will in due time retaliate with symptoms of exhaustion which will express themselves again as an inability to deal in normal time and manner with an average meal. Between the two extremes, appetite, climate, muscular exertion, variety in the dietary, accessibility to food, good or bad cooking, etc., will cause a variation in the daily intake and in the demand made on the function without producing disturbance of the mechanism. This again seems to postulate a " zone " and a " threshold.".

So far as lactation is concerned, the frequency of stimulation held to be desirable for successful exhibition of the function varies considerably. The uneducated mother left to herself feeds her baby "when it wants it," half-hourly, hourly, two-hourly. The Continental school advocates frequent stimulation, every two to two-and-a-half hours. Under Variot's [1] direction "Chaque nourrisson, qu'il soit débile ou normal, est mis au sein 8 fois en 24 heures (toutes les deux heures et demi). . . . C'est à tort qu'on a voulu espacer les tétées toutes les 3 heures et meme toutes les quatre heures." Marfan [2] also recommends 2½-hourly feeding, 7 to 8 feeds per day, with a night feed if necessary. Cathala [3] would go so far as to say that "Au dessous du troisième mois 6 tétées par jour sont un nombre manifestement insuffisant": whereas in Germany Finkelstein [4] and others maintain that a 3-hourly interval providing six feeds "entspricht nur den natürlichen Verhältnissen wenn von den deutschen Kinderärzten diese Zahl der Mahlzeite als die Zwechmässigste empfohlen wird." The English and American habit varies between 3- and 4-hourly, tending perhaps to 4 rather than 3, *i.e.*,5 feeds a day rather than 6. Within these wide limits all are known to have been justified by results. The questions are:—(1) Does this circumstance point to a potential zone of activity for lactation as for other functions? If so, what are its thresholds? (2) Does the result of breast activity as evidenced in the nutrition of the child vary in any degree with the amount of stimulation? (cf. Moore and Dennis [7]: "The most perfectly formed breasts will not function properly without adequate stimulation. This requires emptying of both breasts at least 5 times a day. . . . The supply varies directly with the demand.") (3) Is there within the zone of effective action any point of election which will provide the optimum for both mother and child, nervous as well as physical factors being taken into account; and if this is so, does it indicate a rationale for the management of lactation?

The cases to be recorded were tested from this point of view by an experimental adjustment of feeding times. The babies reached the Centres usually on 3-hourly, occasionally 4-hourly feeds, and the criterion of successful progress in the child, permitting or justifying a change of régime, was held to be, so far as weight was concerned, a regular gain of 6 to 8 ounces per week. No credit,was assigned to any greater increase in weight for the reason that healthy babies surpassing this figure, seemed often to tend to become too heavy, suffering in consequence in appearance, alertness, activity and forward progress at the end of the first year—an opinion frankly contrary to that, for example, of Variot [3], who says, as many do, that the child will do well if allowed to "boire à sa soif," and of Richardson [4] who states that "the breast-fed baby never over-eats, if fed at reasonably long (3 to 4-hourly) intervals." In this series, irrespective of the number of feeds, the efficiency of lactation was held to be established so long as the child gained its 6 to 8 ounces, development was normal and mother and infant were comfortable.

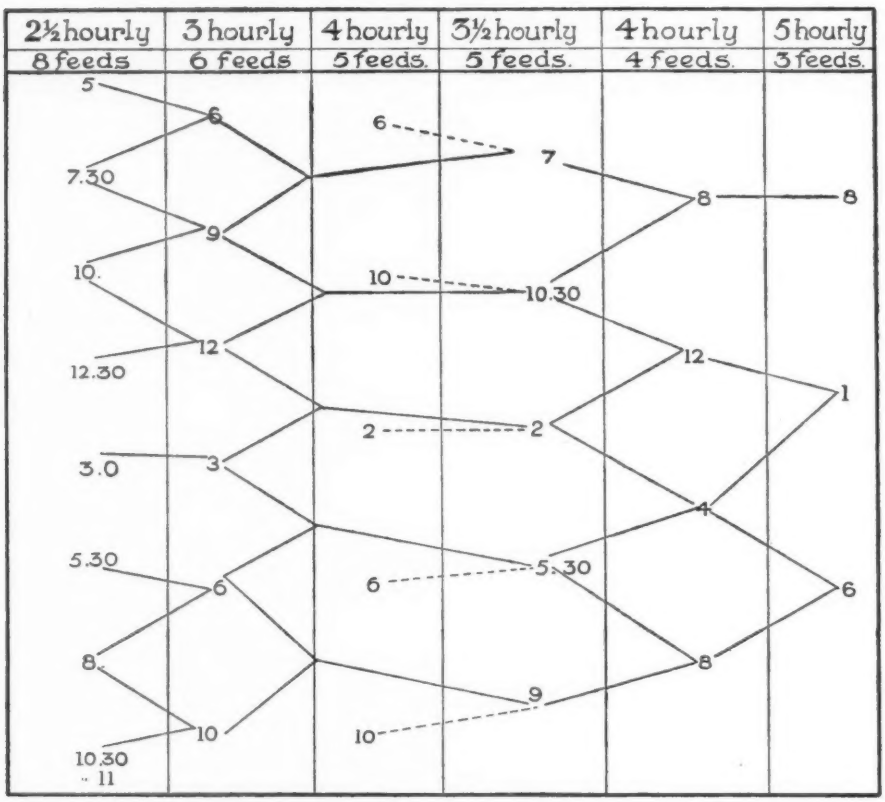
In view of familiar evidence the possibilities of breast feeding under maximal stimulation were not explored. The function was tested for minimal stimulation by reducing feeds from 6 to 5 and then to 4 feeds daily: no

further reduction was attempted below 4 feeds except in the special cases recorded in Series B, when abnormal gain in weight or maternal considerations prompted the further experiment of giving only three feeds daily.

Series A (*Four feeds daily*).

The method of reduction is set out in Time-table 1, which includes also the

TIME-TABLE I.



The figures indicate the hours of the day.

arrangement for the 7 or 8 (Continental), and 3 feeds a day routines, the numbers on the diagram corresponding to the usual hours of feeding during the day. In the earliest cases (1920-21) the transition was not fully accomplished before the sixth month, having then been in part considered as a useful preparation for weaning: and on this account the chart giving the results (Chart I) does not show the figures for 4 feeds a day between birth and that age. As time went on the transition was accomplished more rapidly as lactation showed itself generally capable of proceeding under reduced stimulation, and the children and mothers proved well and comfortable on the smaller number of feeds. The reduction in the number of feeds was completed on occasion by the first month, in cases known to be "good milkers," and frequently by the sixth week. In no case was it attempted without the mother's full understanding and co-operation and in none was there any

record of its being necessary to return to the previous routine owing to poorer gains or the mother's disapproval of the change. As this will indicate, the questions of running away of the milk, over-distension of the breasts, etc., did not give trouble in practice, no doubt owing to the careful graduation of the reduction of feeds. One breast only was used at each feed, and the mothers were instructed to nurse for not longer than twenty minutes.

TIME-TABLE II.

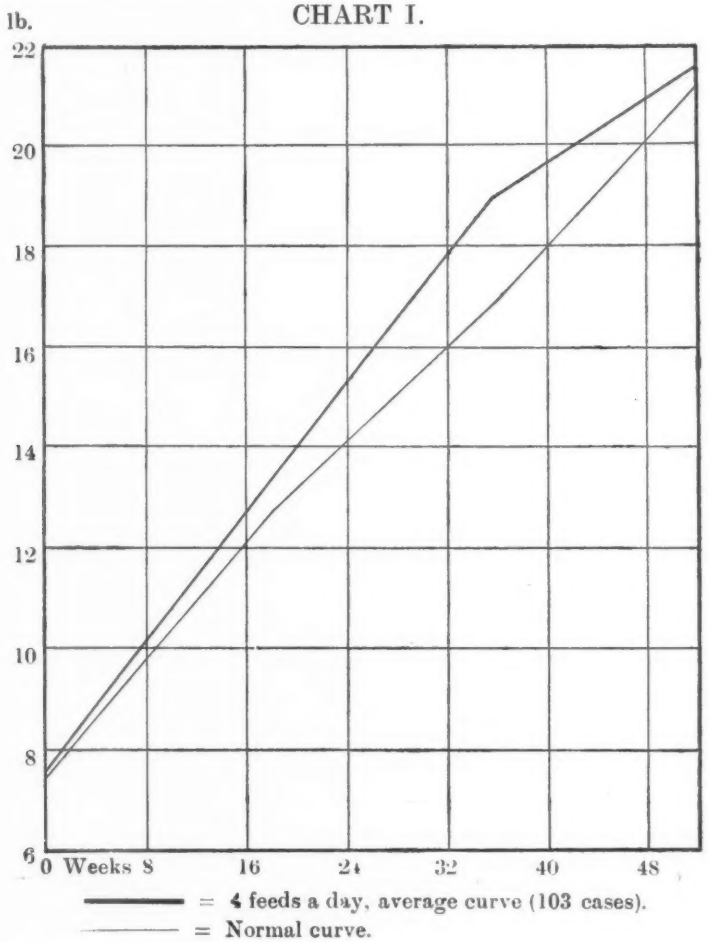
Hour.	Lactation.				Routine arrangements.	Casual Duties.
	2½-hourly (8-9 feeds)	3-hourly (6 feeds)	4-hourly (5 feeds)	4-hourly (4 feeds)		
5 a.m.	X					
6 a.m.		X	X		Rise : early tea. Husband's breakfast.	
7 a.m.	X				School Children's	Washing.
8 a.m.				X	breakfast. Children prepared for school.	
9 a.m.		X			Baby's bath.	
10 a.m.	X		X			Cleaning. Cooking.
11 a.m.						
12 noon	X	X		X	School Children home.	
1 p.m.					Dinner.	
2 p.m.			X		School Children leave.	
3 p.m.	X	X			Baby's walk.	Shopping.
4 p.m.				X	School Children home.	
5 p.m.	X				School Children's tea.	
6 p.m.		X	X		Husband's tea. Baby's bath.	Ironing. Mothering.
7 p.m.					School Children to bed.	
8 p.m.	X			X		
9 p.m.		X			Supper.	
10 p.m.	X		X			Mending and Making.
11 p.m.						
11 p.m.–5 a.m.	(X)				Bed.	

Longest consecutive interval—1½ hours (10·30 a.m. to 12 noon), or if 3-hourly feeds—2½ hours (9·30 a.m. to 12 noon) in which mother has to find time for major work of house, one half-hour being allowed for each feeding, training, and "changing" of baby.

The time-table was arranged so as to procure for the mother maximum relief in the way of night interval and non-interruption of her working periods during the day. The actual transitions by half-hourly intervals were less abrupt than are the ordinary changes from 3- to 4-hourly feeds. The final routine of 4 feeds was arranged so as to correspond with the family meal times, when the mother had in any case to desist from her ordinary tasks. The baby was usually fed then, while the school children were at table, allowing the mother to have her own meal in peace afterwards. It may be noted that special interruptions on behalf of the infant, here absent, are remarkable as a feature of the ordinary 6 feeds (3-hourly) and 5 feeds (4-hourly) régimes, and a glance at the time table of the working woman's day (Time-table II) will show how in this respect the three methods compare.

A collateral enquiry into the composition of the milk and the exact daily intake under these varying régimes would have added to the completeness of the observations, but facilities were not available. Occasional test feeds where carried out showed no undue increase in the amount ingested at one nursing. An analysis of the milk in a 3 feeds a day case seen privately and not reported here showed no abnormality or change in percentage composition.

CHART I.



The progress of 103 cases breast fed on 4 feeds a day is shown in Chart I, where their average weight-curve is compared with the 'normal' curve.

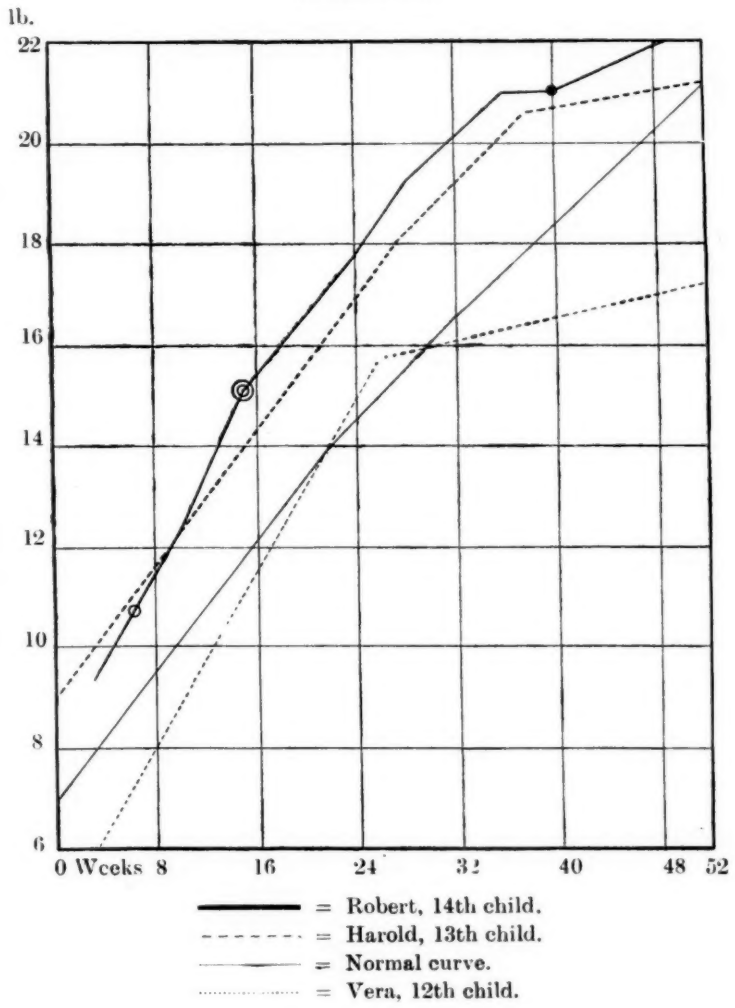
NOTE.—The curve beginning and ending practically on normal level shows between 6 and 8 months when in all cases feeds were restricted to 4 a day, an increase of 1½ and 2 lb. above normal. The figures (in lb. and oz.) are as follows :—

Birth (51 cases)	6 months (103).	8 months (103).	12 months (103).
7·5	16·9	19·0	21·9

Series B. (*Three feeds daily*).

(1) The first case of the 3 feeds a day series is illustrated by Chart II, which gives the weight curves of the 12th, 13th and 14th children respectively

CHART II.

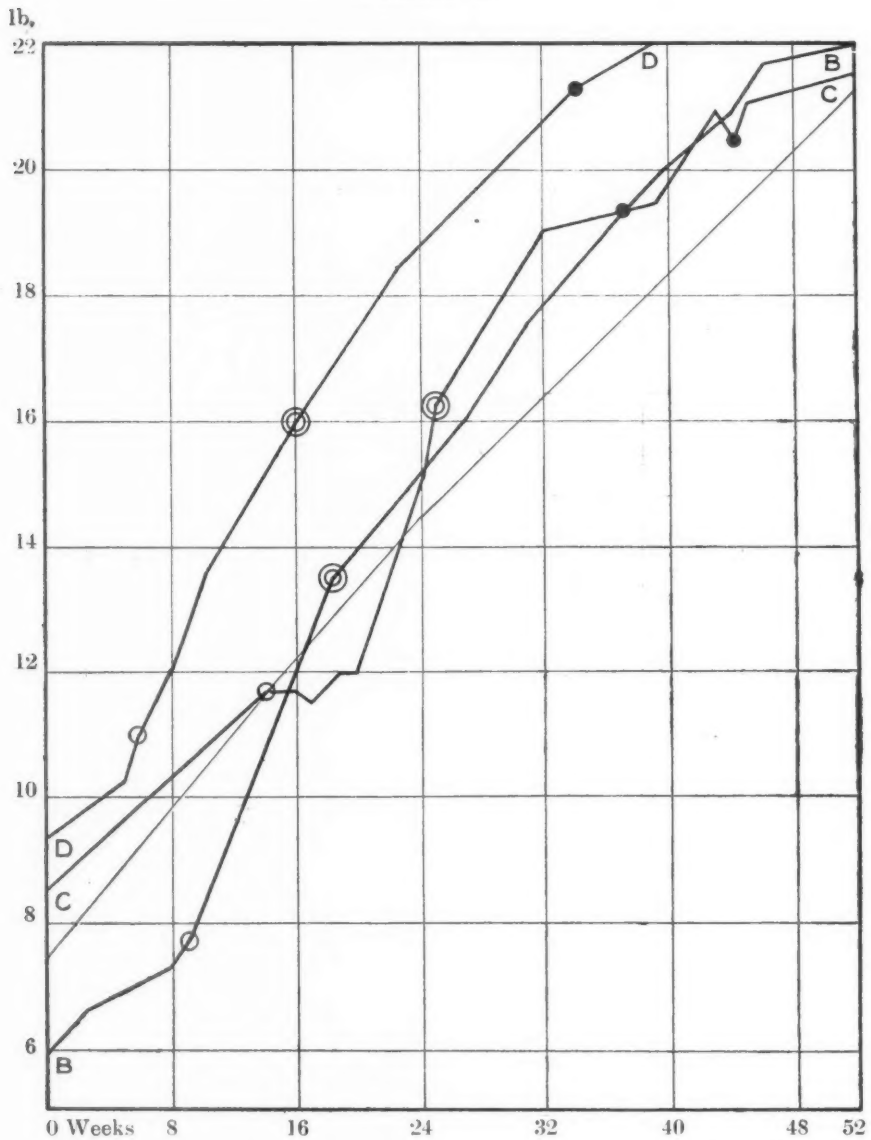


of a multipara of 43 (Coomber). These children were each breast fed according to the routine in vogue at the Centre at the time of their birth, and the four feeds a day régime was instituted at the following ages:—12th child, Vera (1922),

6 months; 13th child, Harold (1923), 3 months; 14th child, Robert (1925), 6 weeks. The birth weight of the child Vera is not known. All previous children had been breast fed.

In all charts the mark O signifies the adoption of a 4 feeds a day routine, ⊙ the progression to 3 feeds, and ● the commencement of weaning.

CHART III.



NOTE.—The curves B, C and D are seen to mount rapidly on a four feeds a day régime, becoming approximately parallel to each other and to the normal when the feeds are restricted to three a day, showing that the requirements of normal nutrition were more nearly met in these cases by the smaller number of feeds.

CASE A. ROBERT COOMBER. 14TH CHILD. (Chart II.)

Mother, aged 43; very bad house in slum street: 4 rooms, 16 people: mother chronic bronchitis and dilated heart: very heavy, cyanosed and breathless: some œdema: husband out of work: milk and dinners allowed at different times.

Baby healthy, gains very well: feeds adjusted to relieve mother as much as possible: 3 feeds only from 16 weeks.

At 6 months, foot burnt.
„ 7 „ otorrhœa: 8 teeth.
„ 9 „ tries to stand.
„ 12 „ 12 teeth: stands alone.
„ 13 „ 15 teeth: walks.
„ 14 „ 20 teeth.

At 9 months the child *Harold* had 4 teeth, and at 12 months 6 teeth.

At 9 months *Vera* had no teeth.

The birth weight of the child *Robert* was less than that of his elder brother; at 7 weeks he passed him and in spite of a reduction to 3 feeds a day, continued at a higher level.

(2) Chart III shows the curves of three cases (B. C. and D.). In two supplementary feeding was eventually replaced by 3 breast feeds a day: in the third, lactation was similarly maintained in order to satisfy the mother's wishes and in spite of her repeated illness.

CASE B. NASH. (Chart III.)

Mother primipara, aged 28: previous miscarriage: supplementary feeds (Nestlé's) started in hospital during first week: mother nervous, thin and anæmic; was convinced breast-feeding was a failure; asked for treatment for her sore nipples and for directions for continuing bottle feeds.

Admitted to Infants' Nursery (special ward) when baby 3 weeks old: breast only 3-hourly (6 feeds) after few days: later 3½-hourly (5 feeds): discharged and seen at Centre at 8 weeks: baby not retaining all feeds.

At 9 weeks still sick, put on 4-hourly feeds (4 per day): mother menstruating.

At 20 weeks 3 feeds per day.

At 5 months "very good, sleeps all time between feeds": at 6½ months slight diarrhœa (hot weather): no teeth.

At 8 months 1 tooth: at 8½ months weaned: at 9 months 2 teeth.

At 11½ months 7 teeth, stands by chair: ant. font. patent.

CASE C. FITCHETT. (Chart III.)

Mother 34, 3 para.: other children 10 and 12: very nervy and thin, almost mental: anæmic, gums spongy: lactation failing: anxious to wean and threatens to discard child.

Seen at 14 weeks. Baby fit but screaming with flatulence: 4 feeds only advised forthwith, simply to induce mother to postpone weaning and to minimise her duties in connection with the child. Supplementary feeds advised to follow breast as necessary.

At 15 weeks lost weight: mother has tried to breast feed and has given no supplementary feeds till last two days: continuing 4 feeds and bottle as before.

At 17 weeks breast only: mother calmer and brighter.

At 19 weeks indigestion.

At 5½ months 3 feeds daily: mother pleased with baby.

At 5¾ months sits alone: in splendid condition. Mother menstruating.

At 7½ months font. small: no teeth: general condition excellent: not gaining much, but mother satisfied with progress.

At 9 months walks by chairs.

At 9½ months first tooth: "climbed 7 stairs to-day."

At 10¼ months 2 teeth.

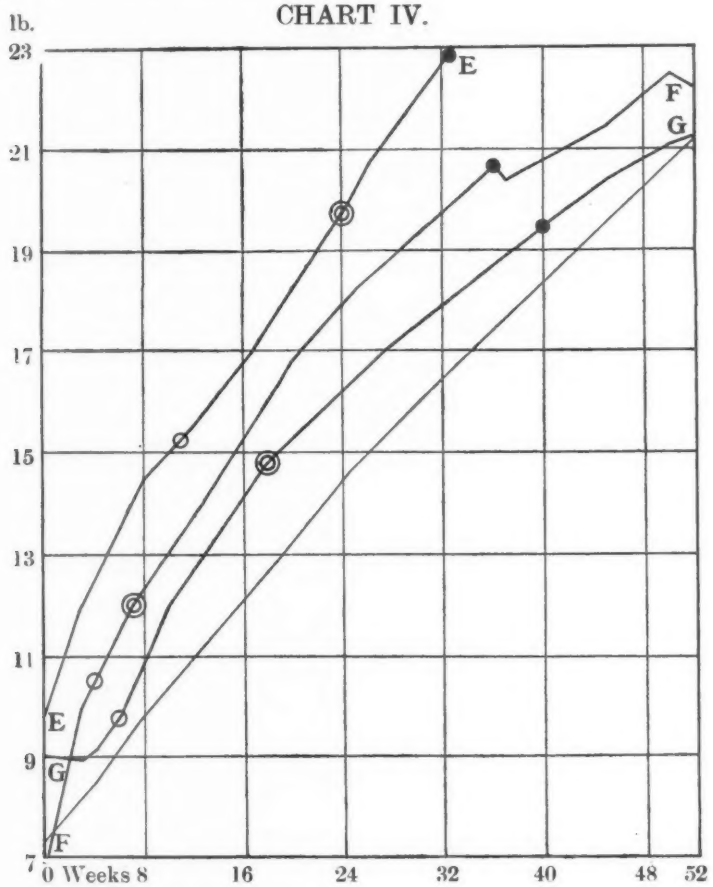
CASE D. O'BRIEN. (Chart III.)

Mother 38: 4-para. last child 9 years: bad teeth: unhealthy tonsils.

At 4 months: mother tonsillitis.

At 4¾ months: mother metrorrhagia: baby on 4 feeds.
At 5 months: big gains: indigestion: 3 feeds. General condition excellent.
At 5½ months: mother tonsillitis.
At 6½ months: mother quinsy, child not disturbed. Very anxious to continue nursing.
At 7½ months: baby sits alone: tries to stand up: 2 teeth.
At 8½ months: mother again unwell: baby weaned.

CHART IV.



CASE E. WHITE. (Chart IV.)
Mother 24: 2 para: last child had spina bifida and died at one year. Dental caries. Baby healthy.
At 11 weeks restricted to 4 feeds a day.
At 5½ months restricted to 3 feeds a day.
At 7 months, 2 teeth.
At 8 months, 5 teeth.
Feeds restricted because of enormous gains in weight.
Did not attend after weaning.

CASE F. LANE. (Chart IV.)
Mother 39: 6-para: big buxom type: husband? T.B. 2 children T.B. glands, all attending T.B. Dispensary.
At 2½ months, 3 feeds daily.
At 4 months, sits up.
At 4¾ months, font. small: very fit indeed.
At 6 months, 2 teeth.
At 11¼ months: 9 teeth: font. closed: walks alone.

CASE G. COPPIN. (Chart IV.)

Mother aged 37: anæmic; tired: third pregnancy: 1 still birth: 1 child 8 years; housing conditions very good: baby ? postmature: "blue baby," 9 lbs. at birth.

At 2½ weeks: sick: diarrhœa: phimosis: to have 5 feeds only.

At 5 weeks: to have 4 feeds. Husband out of work.

At 3 months: milk granted.

At 4 months, to have 3 feeds only.

At 5½ months: mother developed mumps; child vomiting: slight ear discharge.

At 8 months: both sent to convalescent home on mother's account.

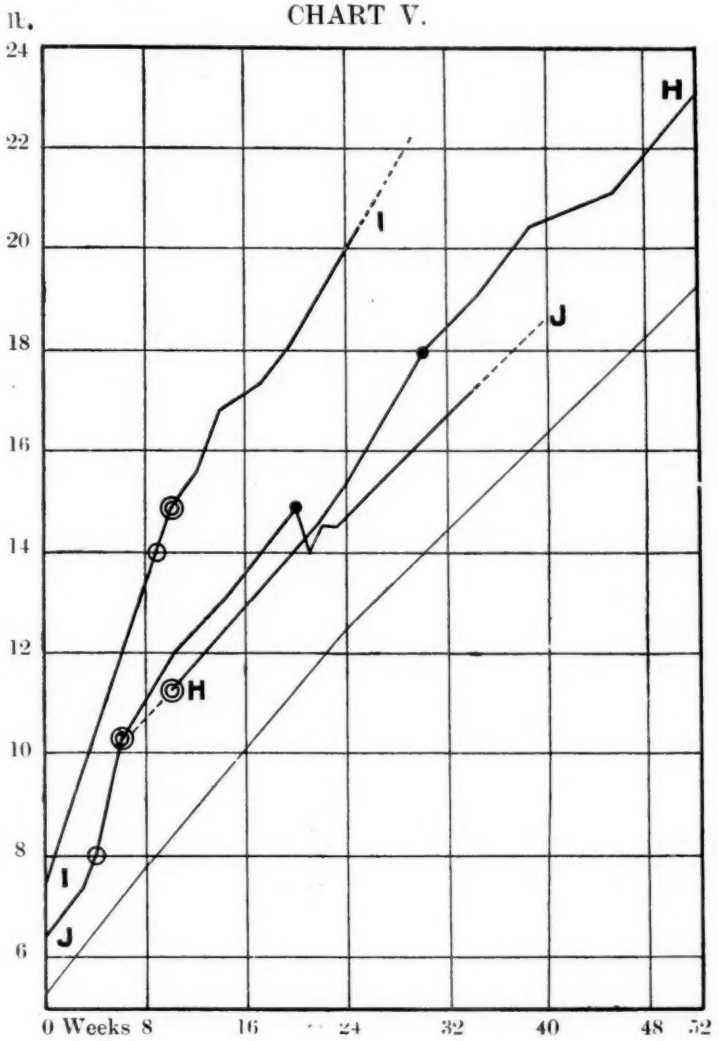
At 8½ months: no teeth: pure Cod Liver Oil started.

At 8¾ months: 4 teeth: font. very small.

At 9¼ months: weaned: 6 teeth.

At 10 months: crawls.

CHART V.



CASE H. KEMP. (Chart V.)

5 people: 2 rooms.

Mother 38: Irish: 3-para: 3 children born in 3¼ years.

First child (girl) now aged 3: 35 lbs.: catarrhal, anæmic, numerous glands: mother thinks backward—says "Must have been overfed as infant" (on 3-hourly feeds).

Second child (girl) now 1 year and 10 months: healthy: on three breast feeds daily under the writer's supervision from 2 months to 6 months: weaned then because of mother's illness, and chart lost since.

At 12 months, walked alone.

At 1 year and 10 months very firm: font. closed: twenty teeth: very talkative.

Third child: boy, Joseph, see chart: 3 feeds routine started by mother herself arguing from satisfactory progress of last child.

At 11 weeks first attended Centre: phimosis noted: mother menstruating.

At 4 months, "splendid."

At 4½ months, sits a little.

At 9 months: 5 teeth: walks a little and tries to talk.

CASE I. MURPHY. (Chart V.)

Mother 35: Irish: fifth child: last 7 years old: house clean, but very poor: father out of work.

At 9 weeks: first seen: excellent condition but fed any time: always crying: constantly at breast: phimosis: 4 feeds advised.

At 10 weeks: gained 12 ozs. on 4 feeds: mother very satisfied.

At 3 months, general condition excellent: start 3 feeds.

At 4 months: bronchial catarrh.

At 5 months: chickenpox: father still out of work. Mother allowed Glaxo for herself.

At 6 months: (up to date of report) very well: no teeth: "mother has plenty of milk."

CASE J. WATSON. (Chart V.)

Mother 25; 2-para: big, strong build, but anæmic at present: several carious teeth: housing, etc., very good. Professedly keen to nurse, but managed last child badly and difficult to reassure about anything. Fine baby.

At 3 weeks: diarrhœa: phimosis: subinvolution.

At 1 month 4 feeds started.

At 7 weeks 3 feeds.

From 11 weeks to 17 weeks in country with mother.

At 18 weeks mother had tonsillitis: smaller gains.

At 20 weeks seen by another doctor: mother insisted on weaning baby against this doctor's advice.

At time of weaning this child was 3¼ lbs. above normal weight, having been ½ lb. above normal at birth.

Remarks on Series B. The cases may be compared with each other in regard to age of mother, place in family and home conditions, and with 'normals' in regard to dental development and progress in activity as well as weight. Notes on these points are to be found in the individual histories. The first two points are perhaps of special interest, and the following table sets out the evidence relating to them.

Name.	Age of Mother.	Place in Family.
White	24	2
Watson	25	2
Nash	28	1
Fitchett	34	3
Murphy	35	5
Coppin	37	2
Kemp	38	3
O'Brien	38	4
Lane	39	6
Coomber	43	14

The variation in age of the mothers covers in the series of 10 cases two decades (24-43 years), or two-thirds of the total childbearing period: the position in family of the children ranges from 1st to 14th. There were

no individual eccentricities in the relationship of these two factors and the average works out at, age of mother 34·1, number of child 4th. It would be difficult to deduce from these figures any direct influence of either age of mother or size of family on the capacity of the individual for maintaining lactation on a régime of greatly reduced stimulation. In 4 cases out of 10, the mother menstruated during her lactation.

Conclusions.

(1) The function of lactation operates successfully within a zone of which the commonly arranged 4-hourly (5 feeds a day) method does not appear to mark the "threshold" in the direction of minimal stimulation any more than the 2-hourly marks it in the direction of maximal.

(2) The nutrition of the child may be adequately secured and lactation may be maintained on a routine of four feeds a day: as a corollary the function responds under the ordinary régimes to a stimulation in excess of what may actually be required for one child.

(3) The 2-, 3- and 4-hourly methods make a considerable demand on the time and energy of the mother considered as a whole and not only in relation to lactation (cf. time-table II.)

(4) A simple re-arrangement and restriction of the number of nursings per day may in conditions of maternal stress, mental or physical or both, have a bearing on the continuance of lactation by alleviating the total demand made on the mother without impairing the health and progress of the child. In certain cases a régime of three breast feeds per day is possible and from the point of view of both mother and child has been shown to have given satisfactory results.

Remarks.

(i.) The condition of the child is usually regarded as the measure of success in lactation, but the comfort of the mother as the chief factor in that success receives in many cases only casual consideration. Ability to nurse has to be decided on an individual basis, and its management must be in line with individual needs. Conventional methods, nevertheless, are judged by their general success in the community, and by the reaction to lactation of motherhood as a whole. Breast-feeding, we find, has not yet been shorn of its difficulties in spite of "Infant Welfare," and professions of allegiance to it, even in Centres, show a discrepancy between creed and accomplishment. Wherein lies the hiatus? What is it that so inhibits a natural process in "Centre" as well as in "outside" mothers? Two suggestions may be made—(*a*) that it is the intelligent, conscientious and eager mother who typically becomes inhibited: (*b*) that a glance at the modern mother's time-table gives an indication of the reason.

The mother's day is composed of duties, interruptions and distractions. At the Infant Centre or elsewhere she is told that the airing and exercising, the cleansing, clothing and changing, the "mothering" of her baby are just as important as giving it its food: and while concerned about the youngest member of the family she is alive to the necessity of looking after the others, sending them clean to school, buying and cooking their proper mid-day dinner,

having the home tidy for them, mending their clothes and supervising personally their bedtime ablutions. In addition she may have a husband to see to, who expects also a reasonable amount of companionship. Anxious, conscientious, and, sooner or later, tired, she performs her duties under continuous pressure. It is in these circumstances that suggestion, not confined to advertisements, may impinge on her mind :—"——builds bonnie babies." "Mothers, nurse your babies : if you *can't*, get——." In one at least of her innumerable functions, and that not the least exacting, it appears that she, the mother, is not irreplaceable ! Discouraged, she tries one, and then two, supplementary feeds, and the result is a foregone conclusion.

The type of mother who is less concerned with her function in life and who is probably unaware of all the things that are implied in really looking after a family, still finds her lactation easy, convenient and cheap. But having striven hard to arouse and educate the maternal conscience we find that this type is now less familiar than that which cannot take things easily.

Arrangements of feeding times which add to the physical and nervous strain of the mother by unnecessary interruption and repetition cannot be expected to improve breast feeding, while other things remain equal : if we do not want to retrogress we must do what we can to relieve the mother, and it is suggested that one step in the right direction may be a general adoption of an easier régime.

(ii.) The chief recommendation for breast feeding is the comparative mortality of breast- and bottle-fed babies. While this seems to ask for more strenuous efforts in promoting lactation in individual cases, it suggests also that the fullest use should be made of mothers of already proved lactatory efficiency. Wet-nursing of premature, marasmic and motherless children, and the avoidance of the dangers of artificial feeding, might become a practicable proposition if under supervision use were made in Infant Centres and elsewhere of married women whose functioning was normal and who could provide for more than their own infant by a sharing of feeds on a 2-or 3-hourly régime. The demands of this double nursing would not exceed what experience has shown that the mammary gland can perform ; and the wet-nurse herself would, in these circumstances, be protected by an alleviation of her other duties and perhaps by pecuniary remuneration, thus precluding the strain which so often causes inhibition in ordinary cases. Constructive work on these and other lines might add to the value of the effort and money expended under the heading of Infant Welfare.

The writer's thanks are due to the Medical Officer of Health for Croydon for his kind permission to compile this report, and to her former colleagues, the Health Visitors, for their generous assistance in the supervision of the cases, and in collating the material for the histories and charts.

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THE FREQUENT OCCURRENCE OF UNDERFEEDING IN EARLY INFANCY.

BY

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In this short paper we shall attempt to prove that in hospital practice the vast majority of infants brought up for gastric symptoms and failure to gain are underfed. This proposition represents an opinion long entertained by one of the writers as a result of his clinical observations, but so far as we are aware, its truth or falsity has not been hitherto tested by a statistical study. We have, therefore, taken one hundred cases from the out-patient notes of patients attending one of us (D.P.) at The Hospital for Sick Children, Great Ormond Street in 1926 and 1927. We should like to emphasise the fact that the hundred cases discussed were taken indiscriminately and not specially selected.

Infants from the age of six months downwards were regarded as best illustrating the object in view, and both the breast-fed and the artificially-fed have been considered.

An important point must be remembered in estimating the gains in weight after the correction of the diets, *i.e.*, that every infant, unless definitely suffering from a fat-diarrhœa, was ordered cod liver oil emulsion. A grain of chloral hydrate was also given three times daily for a period of one week.

Breast Fed Infants.

Group I. Underfeeding on the Breast.

In our series there were 28 of the above type, 15 males and 13 females.

Sex.	Av. birth wt.	Av. age at examination.	Av. wt. at examination.	Av. gain per week after correction of feed.	Approx. "below level" weight.
M.	7 lb. 6·8 oz.	9·46 weeks	8 lb. 13 oz.	11·25 oz.	2 lb. 15 oz. per infant.
F.	7 lb. 3½ oz.	12 weeks	9 lb. 8 oz.	10·71 oz.	3 lb. per infant

The routine adopted was the giving of complementary feeds, that is, additional artificial feeds immediately after the breast. In no case was the child taken off the breast. In making the diagnosis a test feed was invariably carried out.

Among these 28 cases were three of about six months who obviously wanted a starch complement (groats, soup, etc.), while in another infant of two months the mother, though short of breast milk, was very irregular in giving the complementary feed, with the result that the infant gained only 5 oz. per week.

One infant of 4 months was suffering from diarrhœa and vomiting which disappeared when a thick complementary feed was given.

Only one case of breast-fed rickets was recorded, an infant of 4 months, who did well on a complementary diet in the form of starches, such as groats, patent barley, cream of rice, Allenbury's No. 3, bone and vegetable soup, etc.

Apart from failure to gain. "air swallowing" in these hungry babies probably accounted for the three other chief symptoms commonly noted, viz., vomiting, screaming and frequency of defæcation. The underfed infant, being left at the breast longer than is necessary, tends to swallow wind; that is, having obtained all the mother's supply in say 2 or 3 minutes, for the next 5 minutes continues to suck and at the same time swallow air. The following sequence of events then occurs. The stomach being fully distended, the child feels comfortable and dozes at the breast, appearing satisfied. A portion of the swallowed air passes through the pylorus into the bowel, producing increased peristalsis by distending the bowel. The result is frequent, small, explosive motions each time the infant is placed to the breast. The portion of the air remaining in the stomach is eructated and some of the food is brought up with it.

Example. A male infant, L.R., birth weight 8 lb. 5 oz. presented itself at the age of 5 weeks weighing 9 lb. 4 oz. The child was entirely breast fed, and a test feed showed an insufficiency of breast milk. Complementary feeds of cow's milk and water were added and there was a gain of 11 ozs. in the following 7 days. *Diagnosis*—underfeeding on the breast.

Group II. Overfeeding on the Breast.

Only one case was met with in an infant of eleven weeks of age, weighing 12 lb. 14 oz., which, on having its feed regulated and reduced stopped screaming and continued an average increase weekly.

Overfeeding on the breast is said to be extremely common. Whether this be so or not we offer no opinion, but we would deny that serious pathological disturbances are produced in any number of infants by overfeeding on the breast. In this large series of ailing infants we are only able to record one case, although the possibility was always present to our minds. The infant who is being overfed on the breast would seem to adjust itself rapidly to its feed by occasional small vomits and an increased number of stools. The gain in weight in the overfed infant on the breast is as a rule excessive.

Group III. Underfeeding in Breast-fed Infants, already having complementary feeds.

In this class there were eight cases, presenting themselves with different forms of gastric disturbance and failure to gain. Three, apart from the breast,

were having complementary feeds of Cow and Gate, one Nestlé's, one Almata, one Allenbury's, one cow's milk and one cow's milk and Virol.

Av. birth wt.	Av. age at examination.	Av. wt. at examination.	Av. gain per week after correction of feed.	Approx. "below level" weight.
7·96 lb.	14 weeks	10·98 lb.	8·53 oz.	2 lb. 10 oz.

It will be noticed that the average age and weight at the examination is higher than in the first-class (purely breast fed) owing no doubt to the fact that the mother in each case was aware of the deficiency in her breast milk and attempted complementary feeding for some time of her own accord before bringing the infant up to Hospital.

Example. A male infant, C.S., birth weight 7 lb. 10 oz., was seen at the age of 10 weeks weighing 10 lb. 6 oz., fed at the breast and getting complementary feeds of Allenbury No. 1. The symptoms complained of were flatulence, irritability and failure to thrive. A complementary feed of cow's milk, water and sugar was given and there was a gain of 17 oz. in 14 days. *Diagnosis*—underfeeding on the breast, with insufficient complementary feeding.

Group IV. Rumination Cases (Merycism).

Four of these cases are included in our series. One was being fed on Glaxo, one on peptonised cow's milk, one on cow's milk and another on the breast, with a complementary feed of Nestlé's.

The average weight at birth was 8 lb.
The average age at examination was 18·5 weeks.
The average weight on examination was 9 lb. 6 oz.
The average gain per infant per week after correction of diet was 15·66 oz.

Alteration in the diet was made by thickening the feeds in all four cases, and the enormous average gain was very gratifying. One infant actually put on 28 oz. in 7 day, another 25 oz. in 7 days. The approximate "below level" weight for this class at their average age was 6 lb. 2 oz. per infant.

It would appear to us that this class of case tends to go undiagnosed. The clinical picture is clear cut. The infant fails to gain weight, the vast majority being extremely bright infants, more often females. The initial feed is often of a sweet nature and too large in amount, tending to cause regurgitation. The habit of regurgitating the food is thus formed by the infant, and quite rapidly some of each feed is regurgitated at intervals, until the stomach is empty, or until the time of the next feed. The mother's complaint is that "the pillow is always wet," although she seldom complains of large vomits. The result of giving thickened, concentrated feeds is dramatic, as shown by our figures.

Example. A female infant, M.E., birth weight, 6 lb. 14 oz., was seen at the age of six months, weighing 7 lb. 3 oz. She had been fed up to this time on cow's milk, water and sugar

and the complaint was of continual vomiting and wetting her pillow. She was put on a cow's milk and water feed, thickened with Benger's Food; small, thick, concentrated feeds; 28 oz. were gained in 7 days. *Diagnosis*—Rumination.

Group V. Congenital Hypertrophic Pyloric Stenosis.

Included in this series were nine cases of the above condition. All were admitted to Hospital for operation. It is most interesting to note that all were males and seven were breast fed. One was having Cow and Gate milk, and the remaining one a cow's milk mixture. Unfortunately in two or three instances the birth weights were not recorded, but in these we have put them at 7 lb.

The average age at examination was 6·22 weeks.
The average birth weight was 7 lb. ·44 oz.
The average weight at examination was 7 lb. 1 oz.

The almost negligible gain at the average age of six weeks is perhaps pathognomonic of the condition. The approximate "below level" weight for this class at their average age was 2 lb. 7 oz. per infant.

Artificially Fed Group.

Babies who were entirely artificially fed formed, curiously enough, exactly half of the series of a hundred cases. They presented much the same symptoms and physical signs as the breast-fed cases, but to one of us (A.M.G.), accustomed in South Africa to meet severe diarrhœa in large numbers of artificially-fed infants, the mildness of the diarrhœa or the actual absence of this symptom was striking.

Among the 50 artificially-fed cases there were only two that could be classified as overfed. One was definitely so on cow's milk and sugar, the other was having a full-cream dried milk and was obviously suffering from fat-diarrhœa.

A great similarity will be noticed between the purely breast-fed, the partially breast-fed, and the artificially-fed infants, in that the majority were being underfed either in quantity or quality, and on the increased and balanced diets the weekly weights rose with automatic regularity.

Twenty-seven of the fifty are included in a class (Group VI) as "under-caloried" and these are infants who, at examination, were found to be on a diet deficient in all three elements, carbohydrate, fat and protein.

Sixteen are classified as "under-caloried" generally, but especially in carbohydrate" (Group VII) and four as "underfeeding on carbohydrate only" (Group VIII). Two were overfed (Group X) as mentioned above and one was a well marked case of rickets on an under-caloried diet (Group IX).

In Group VII (the under-caloried generally, but especially in carbohydrate) most of the infants were on dried milks or a cow's milk mixture, with little or no additional sugar.

In the "under-caloried" an increase in the amount of the feed was usually all that was required. The routine in dealing with the artificially underfed was to leave the infant on the feed which it was having, but to increase or alter

the feed suitably so that its balance was adjusted. The only exception to this was in those cases in which we were dealing with a synthetic dried food.

A number of dried milks are sold to the public with inadequate directions on the tin. Some advocate feeding by age, thus grossly overfeeding the infant born small and weakly, or grossly underfeeding a large and robust infant. The second gross error in these directions is that in the majority the addition of sugar is not mentioned. When it is considered that a heaped teaspoon of the average dried milk added to one ounce of water reconstitutes an ounce of cow's milk, it will be seen that if sugar be not added the infant is being fed on plain cow's milk. The balance of the various elements in cow's milk does not produce an optimum gain in weight, as it is by itself a ketogenic or bilious type of diet. Extra carbohydrate in the form of sugar or starch must be added to metabolise the fat present. Full-cream dried milks should include in their directions the addition of carbohydrate in the form of sugar. We enumerate 20 cases where the chief feature was the badly balanced diet, the deficiency being in carbohydrate.

Group VI. The Under-caloried in carbohydrate, fat and protein.

There were 27 cases of this type, 12 males and 15 females. No difference worthy of record was noticed between the two sexes.

Av. birth wt.	Av. age at examination.	Av. wt. at examination.	Av. gain per week after correction of diet.
7 lb. 8 oz.	10·88 weeks	8 lb. 14 oz.	11·06 oz.

The approximate "below level" weight for this class at their average was 2 lb. 14 oz. per infant.

Example.—A female infant, A.B., birth weight 8 lb., was seen at the age of 16 weeks weighing 8 lb. ½ oz. Feed up to this time, Almata, 3 teaspoons, water, 6 tablespoons, six feeds, three-hourly. The complaint was of wasting, constipation and vomiting. The child was put on an adequate cow's milk, water and sugar feed with a resulting gain of 19½ oz., in the first 7 days. *Diagnosis*—Under-caloried on protein, fat and carbohydrate.

Group VII. The Under-caloried generally but especially in carbohydrate.

Sixteen of these cases presented the following averages :—

Av. birth wt.	Av. age at examination.	Av. wt. at examination.	Av. gain per week after correction of diet.
8·562 lb.	14·25 weeks	10·75 lb.	10·72 oz.

The approximate "below level" weight for this class at their average was 4 lb. 4 oz. per infant.

Example. A male infant, C.J., birth weight 10 lb., was seen at the age of 12 weeks weighing 10 lb. 8 oz. The feed up to this time had been cow's milk and water with no sugar. The complaint on coming to Hospital was that the child did not gain. The cow's milk was increased and sugar added; 31 oz. were gained in 14 days. *Diagnosis*—Under-caloried generally, but especially on carbohydrate.

Group VIII. Underfeeding on Carbohydrate only.

All four of these cases were on dried milks, without the addition of sugar.

Av. birth wt.	Av. age at examination.	Av. wt. at examination.	Av. gain per week after correction of diet.
6 lb. 8·75 oz.	10·28 weeks	8 lb. 13·25 oz.	14·56 oz.

The approximate "below level" weight for this class at their average age was 2 lb. 3 oz. per infant.

Example. A female infant, J.T., birth weight 7 lb. 2 oz., was seen aged 10 weeks, weighing 9 lb. 5 oz. She had been fed up to this time on Cow and Gate milk, with no added sugar. The complaint was of constipation, and occasional vomiting. No change in the feed was made beyond the addition of sugar, with the result that the infant gained 13½ oz. in 7 days. *Diagnosis*—Underfeeding on carbohydrate only.

Group IX. Under-caloried, with florid rickets.

The one case of this type was a four months' infants of 12 lb. in weight. It had sweating of the head, was very restless and the mother said it was screaming continually. When examined well-marked cranio-tabes was found. Its feed had been cow's milk and a well known cod-liver-oil-free proprietary preparation reputed to cure rickets.

Group X. Overfeeding (artificially fed).

Only two out of the series could be included in this class.

One was a male infant, birth weight 6 lb. 9 oz., who was seen with diarrhœa and vomiting. At the examination his weight was exactly the same as at birth. He was being fed on a full cream Cow and Gate feed with no sugar added. Put on to half cream Cow and Gate plus sugar with each feed, his diarrhœa and vomiting stopped and he gained 8½ oz. in 7 days.

The other case of overfeeding is well worth recording, since she was on a feed representing 1½ pints of cow's milk in 24 hours and having 2 drachms of sugar with each feed—8 feeds in the 24 hours. She was 11 weeks old, weighed 7 lb. 8 oz. at birth and was 9 lb. 3 oz. at examination. The cow's milk and sugar was reduced and later thickened and she put on 13 oz. in 11 days, becoming happier and more comfortable.

Comparisons in "below-level" weight at the time of examination.

The average weights of these infants suffering from underfeeding at the times of examination compared with their birth weights and their respective ages make interesting and instructive reading.

Group.	No. of cases.	Average weight below normal.
I. Underfeeding on the breast	28	2 lb. 15½ oz.
III. Underfeeding on the breast, with complementary feeds..	8	2 lb. 10 oz.
IV. Rumination	4	6 lb. 2 oz.
V. Congenital hypertrophic pyloric stenosis	9	2 lb. 7 oz.
VI. Artificially fed: Under-caloried in carbohydrate, fat and protein	27	2 lb. 14 oz.
VII. Under-caloried generally, but especially in carbohydrate	16	4 lb. 4 oz.
VIII. Underfeeding in carbohydrate only	4	2 lb. 3 oz.

Compared with the average gains per infant per week it is interesting to note that where there was the greatest deficit there was the correspondingly highest gain after treatment. For instance in the rumination cases, the average weight below the normal was 6 lb. 2 oz. and after treatment the average gain per week was 15·66 oz.

It will be clear to anyone reading these notes that certain infants attending the hospital have been excluded. Infants brought up for organic disease, such as congenital heart disease and other malformations, have not been included, nor have those infants with severe digestive upsets who had to be admitted immediately. It is of interest to remark that in the year 1926 and half the year 1927, out of some 4,000 new attendances up to the age of 12 at the clinic of one of us (D.P.), not more than half a dozen cases of severe diarrhœa and vomiting was seen. The infant feeding and nutritional problems, therefore, are entirely different in London from those met with in parts of America and other parts of the world where the climate is warm.

Discussion.

The idea that under-calorie-ing, or starvation, or underfeeding is common in hospital patients is not a new one. Fleming and Hutchison (1) recently showed by careful study of the metabolism of similar cases in Glasgow that the digestion and absorption of the various food elements was perfect, and concluded that the chief error in these wasted infants was in under-calorie-ing, and especially in a deficiency of carbohydrate in the diet. Parsons in his Goulstonian Lectures (2) suggests that in the marasmic infants which he studied carefully, the various food elements were readily absorbed and especially so the fat, although he admits that clinically fat is not well managed in wasted infants. Marriott (3) considers that a very common error in feeding the child who is much under weight is made by under-calorie-ing. Often a very wasted infant requires almost double the caloric requirements of a normal infant. We would suggest that the terms " dyspepsia," " marasmus " and " indigestion" are too readily used ; such terms are vague and to us unjustified.

Summary.

In a series of 100 under-weight infants investigated suffering from gastric symptoms and failure to gain in weight, 50 were wholly or partially breast fed and 50 were artificially fed.

Breast Fed Infants.

1. Twenty-eight cases were definitely underfed on the breast, but when given complementary feeds gained an average 11 oz. during the first week.

2. Eight cases were underfed on the breast, but were already having complementary feeds. In these the augmenting of the complementary feeds produced an average gain of 8 oz. in the first week.

3. Overfeeding on the breast was observed in one case only in a series of 50 breast fed infants. This bears out the impression that overfeeding on the breast, producing severe disturbance, is a rarity.

4. The most markedly subnormal cases were those of rumination. Dramatic improvement occurred on thickened feeds.

5. Congenital pyloric stenosis was found in 9 of the 50 cases.

Artificially Fed Infants.

6. Twenty-seven of these 50 infants were merely under-caloried or starved.

7. There were 16 starved or under-caloried, but especially in carbohydrate.

8. In 4 cases the feed was quite sufficient except in carbohydrate, where there was a gross deficiency.

9. In only one case was there florid rickets. One might have expected a larger number, but the infants, it must be remembered, were very young and were generally underfed.

10. Overfeeding was met with in two cases only, one of which showed fat dyspepsia and the other gross overfeeding with all elements in the diet.

11. Of the 100 cases studied 84 per cent. were under-caloried; 3 per cent. were overfed and 13 per cent. were being starved, the cause being either organic (congenital pyloric stenosis) or functional (ruminations).

Conclusion.

From the above examination of this series of 100 cases, and from the figures arrived at, we feel justified in concluding that the chief cause of gastric symptoms and failure to gain in weight in hospital out-patient infants under six months is starvation.

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ON THE CLINICAL VALUE OF BLOOD ANALYSES IN NEPHRITIS IN CHILDHOOD.

BY

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The following analyses (Tables I and II) confirm the work of previous investigators. The series is, however, fairly extensive, and serves as the basis of a short discussion on the value of such estimations in clinical medicine.

Urea was estimated by the urease method, using 3 c.cm. of blood. Cholesterol and plasma proteins were determined colorimetrically, according to the techniques of Myers and Wardell[2], and of Wu[3] respectively. The tables are self-explanatory.

TABLE I.

Blood Cholesterol and Urea in Nephritis.

DISEASE.	Age: Years.	No. of cases.	mgm. per 100 c.cm. whole blood. Cholesterol Lowest	Cholesterol Highest	Cholesterol Average	Urea Lowest	Urea Highest	Urea Average
Normal.*	$\frac{5}{12}$–13	38	105	214	**165**	21	58	**38**
Acute Nephritis	1–10	18	131	315	**182**	28	255	**67**
Hæmorrhagic nephritis	4–11	9	126	231	**166**	28	85	**52**
Chronic azotæmic nephritis (chronic interstitial nephritis§	1–11	11	114	294	**193**	41	692	**289**
Mixed azotæmic and hydræmic nephritis	2–15	7	154	810	**316**	53	297	**112**
Chronic hydræmic nephritis (chronic parenchymatous nephritis or nephrosis)	1–8	9	279	791	**479**	20	31	**26**

*Many of these were convalescent surgical cases. The rest were medical cases, excluding renal diseases and all conditions in which hypercholesterolæmia might be expected (e.g. diabetes mellitus, hepatic lesions, xanthomatosis, etc)..

§Most of these cases were renal dwarfs.

SUMMARY.

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Chronic hydræmic nephritis (chronic parenchymatous nephritis or nephrosis)	1–8	9	279	791	**479**	20	31	**26**

*Many of these were convalescent surgical cases. The rest were medical cases, excluding renal diseases and all conditions in which hypercholesterolæmia might be expected (e.g. diabetes mellitus, hepatic lesions, xanthomatosis, etc)..

§Most of these cases were renal dwarfs.

TABLE II.

PLASMA PROTEINS IN NEPHRITIS.

No of Cases.	Sets of Analyses.	Types of Nephritis.		Age	mgm. per 100 c.cm. whole blood.		Plasma proteins gm. per 100 c.cm. plasma				Globulin % of protein.
					Urea.	Cholest.	Fibrin.	Alb.	Glob.	Total	
8	10	Acute	Min	1	25	145	0·247	2·84	1·76	5·02	25
			Max	10	105	315	0·745	5·04	3·15	8·27	49
			Av	—	**57**	**182**	**0·460**	**4·16**	**2·41**	**6·93**	**35**
7	8	Acute Hæmorrhagic	Min	4	23	129	0·282	3·91	2·02	6·99	26
			Max	10	73	231	0·575	5·47	2·97	8·66	39
			Av	—	**44**	**171**	**0·446**	**4·80**	**2·47**	**7·72**	**32**
4	4	Chronic Azotæmic (chronic interstitial)	Min	1	41	119	0·380	3·19	1·28	5·82	16
			Max	12	592	201	0·613	6·00	3·55	8·40	44
			Av	—	**297**	**165**	**0·524**	**4·40**	**2·29**	**7·21**	**31**
3	4	Mixed Azotæmic and Hydræmic	Min	5	40	190	0·400	2·14	1·87	4·54	31
			Max	10	297	261	0·772	4·43	3·50	8·33	42
			Av	—	**140**	**231**	**0·555**	**3·43**	**2·51**	**6·50**	**38·5**
5	6	Chronic Hydræmic (chronic parenchymatous or nephrosis)	Mini	2	20	279	0·370	1·51	1·10	2·61	42
			Max	8	39	666	0·656	2·58	2·59	5·55	51
			Av	—	**29**	**436**	**0·519**	**2·01**	**1·96**	**4·18**	**46·5**

The results have been collected from the records of the Hospital for Sick Children, Great Ormond Street, over a period of two years (1925 and 1926). One of us (G.A.H.) collected the laboratory data, and sent the names of the patients to the other (W.G.W.), who tabulated the cases, according to the types of nephritis they presented on clinical examination. The great majority of the patients had been under observation during the time when one of us (W.G.W.) was Medical Registrar to the Hospital. The classification of the different types of nephritis is therefore according to a uniform plan (see [4]). No doubt in certain instances the laboratory data influenced the actual labelling of the case when in hospital, but by reviewing our results after an interval in the way described, we think the risk of making the diagnoses fit the figures has been reduced to a minimum.

Blood Cholesterol Estimations.

It will be seen from Table I, that the *average* blood cholesterol for the different groups agrees with accepted teaching. If, however, the *ranges* for the several groups are compared, it will be seen that the cholesterol content of the blood may be of very little diagnostic value in an individual case. It may be concluded that figures over 300 mgm. per 100 c.cm. are practically confined to the hydræmic types of nephritis. In all these cases the œdema was of a gross character, and the cholesterol estimation was really superfluous from the point of view of classifying the type of nephritis. Cholesterol estimations afford no means of distinguishing between those cases which have

commenced as nephrosis, and those which may be called chronic parenchymatous nephritis or nephrosis, but which have developed subsequent to an attack of acute nephritis. The initial inflammation of the kidney in the latter type having passed off, it is probable that the later state of the kidney is the same in both classes. It is interesting to note that marked hypercholesterolæmia may be associated with nitrogenous retention, and is not confined to cases of nephrosis. Figures under 300 mgm. per 100 c.cm. may be found in any of the different groups, and are then of no value in assessing the type of nephritis.

On the whole we have found that the cholesterol estimations are of little or no practical value in the diagnosis, prognosis or treatment of nephritis in children.

Blood Urea Estimations.

The importance of estimations of the urea content of the blood is of course well established, and needs no further elaboration. One point, to which we wish to draw attention, is that the normal range for children under twelve is apparently higher than that for adults by some 10 mgm. per 100 c.cm. In this respect the young are like the old, though the cause of the higher figures at the extremes of life is presumably different. The metabolism of children is more vigorous than that of adults, and this may be the cause of the higher figures in the former group. In old age the higher blood urea is probably due to the kidneys being less efficient than in young and adult life.

Determination of the blood urea-content is the only sure method of discriminating between *mixed azotæmic plus hydræmic* and *chronic hydræmic* nephritis. Oedema may be almost as gross in the first as in the second. The mixed form, in fact, in the absence of red blood corpuscles in the urinary deposit, or possibly cardio-vascular changes, is often clinically indistinguishable from chronic hydræmic nephritis. A high figure, therefore, for the blood urea in a chronic œdematous case is certain evidence of interstitial plus parenchymatous change in the kidneys. The point is of prognostic importance, the outlook being decidedly less favourable in the mixed form of nephritis.

As regards the general utility of blood urea estimations, our experience agrees with the general consensus of opinion, that they are often invaluable in the diagnosis, prognosis and treatment of nephritis.

Differential Estimations of Plasma Proteins.

Table II shows the findings for the differential estimation of the plasma proteins in the nephritides of children. It will be seen that the percentage of fibrin is almost invariably raised in all types. There would appear to be no special value in this particular analysis. The usual value for this constituent normally lies between 0·20 and 0·38 per cent.

The values for albumin, globulin, total protein, and globulin percentage of the total protein, for the three groups, " acute," " acute hæmorrhagic," and " chronic interstitial," generally fall within the normal limits, as given by previous workers. The normal limits are : albumin 4·5 to 6·7, globulin 1·2

to 2·7, total protein 6·7 to 8·6 per cent., and globulin, as percentage of total protein, 16 to 40 per cent. The two groups of hydræmic nephritis alone remain for consideration. It will be seen that our results simply confirm previous work in that the total protein is decreased, and that this decrease is more at the expense of the albumin than of the globulin fraction. We have not, however, observed such extreme losses of albumin as those recorded by Epstein[1].

The average composition of the sera in Epstein's cases is given in Table III for comparison.

TABLE III.

EPSTEIN'S ANALYSES FOR COMPARISON WITH TABLE II.

Sera.	Gm. per 100 c.cm.			Globulin per cent.
	Total	Albumin	Globulin	
Normal	7·400	4·662	2·738	37·0
Cardiac conditions	6·408	4·417	2·240	33·9
Chronic interstitial nephritis	6·704	4·310	2·396	35·7
Chronic parenchymatous nephritis	3·928	0·466	3·462	89·2

Our results apply to the plasma, and therefore include fibrin, whereas his figures are for sera. The fibrin, however, is but a small percentage of the total protein, and so we have not recalculated our globulin percentage in terms of the *serum* total protein as opposed to the *plasma* total protein. It will be seen that in Epstein's cases of chronic parenchymatous nephritis the average globulin content is actually higher than in the normal group, whereas in ours it is a little below the normal. This fact, coupled with the lesser loss of albumin in our cases, accounts for the marked difference between the globulin per cent. of total protein in the two series: 89·2 in Epstein's series as against 46·5 (or 46·9 if expressed as percentage of the *serum* total protein) in our series.

The changes in the plasma proteins in the group of mixed azotæmic and hydræmic nephritis are similar to those in the group of chronic hydræmic nephritis, though less marked in degree.

Our opinion as to the clinical value of estimations of the plasma proteins is the same as that expressed for cholesterol determinations. The analyses are really superfluous. Grossly abnormal figures only occur in nephritis with marked œdema. That does not imply, of course, that all cases of severe œdema of whatever origin will invariably show these changes. Patients, for instance, with purely cardiac œdema may not, but there is no need to make a differential estimation of the plasma proteins in order to distinguish cardiac from renal œdema. In our experience, these protein analyses are of little or no help clinically in the diagnosis, prognosis or treatment of nephritis.

We do not wish to give the impression that we regard much of the biochemical work of the above nature as altogether useless. It has undoubtedly played an important part in studying the pathology of œdema, etc.,

etc., and such analyses will continue to be of value in research work. It is, however, of advantage to the clinician to realise what chemical tests are of value to him in the care of his patients, and it is also desirable that the laboratory worker should not be overburdened with lengthy analyses, which will be of no practical use to his clinical colleague. Co-operation between clinician and laboratory worker is essential, both in planning work which will assist in the improvement of a patient's condition, and in undertaking investigations which may lead to new knowledge of disease and its pathology.

We wish to thank those members of the Staff of the Hospital, to whom we are indebted for the use of cases, and Mr. R. J. Bromfield and Miss E. M. Taylor for their technical assistance.

Summary.

1. The cholesterol and urea content of whole blood has been determined, and a differential estimation of the plasma proteins has been made in a series of cases of nephritis. The results confirm the work of previous investigators.

2. As a guide to the clinical control of a case the urea estimations are often of great value; the cholesterol and plasma determinations are generally superfluous.

3. As an aid to the classification of the type of nephritis, the same conclusion applies.

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AN INVESTIGATION INTO THE INCIDENCE OF HERNIA IN CHILDREN.

BY

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Statistics from the British Isles on the incidence of hernia on a large scale are few. Certain facts have been stated and textbooks have repeated them without confirmation. To verify or impugn the accepted figures we have undertaken to investigate 1018 cases of hernia presenting themselves at the Out-Patient Department of the Hospital for Sick Children, Great Ormond Street. The period covered includes the years 1919, 1921, 1922, 1923, and 1924; and concerns the children up to the age of three years presenting themselves with inguinal hernia during this period. As regards umbilical hernia all cases during this period up to the age of 12 years were investigated.

Incidence of Hernia in Children of the Hospital Class. The number of new out-patients during the five years was 130,243, and of these 1018 were suffering from hernia of some variety, that is, an incidence of 0·8%. The *sex incidence* showed 838 males (79%) and 180 females (21%).

Inguinal Hernia. Out of 1018 cases there were 773 simple inguinal herniæ. 696 cases were males and 77 were females, that is, 90% were males and 10% females.

Operations and Recurrences. Out of the 773 inguinal herniæ, 564 were operated upon, with 4 recurrences. This is a proportion of 0·7%. Of the 209 cases which were not operated upon, in 185 the hernia had apparently spontaneously disappeared, while in 24 the hernia was still present, but not operated upon for some special reason of the parents or the condition of the child.

Incidence of Spontaneous Cure of Inguinal Hernia. Out of the total of 773 inguinal herniæ investigated, 185 disappeared spontaneously. This is 24% or one quarter did not require operation.

The chances of a spontaneous disappearance of an inguinal hernia would appear to be better in females than in males, since in 37% of females but only in 22% of males did this occur.

That these figures represent only apparent cures must be emphasized; as in contrast to umbilical hernia where one can by a truss or pad invaginate and thereby obliterate the sac, thus being certain of cure, in inguinal hernia the word "cure" merely signified in many cases a fibrosis of the neck of the sac, a potential hernial sac still existing. It may be that from these apparent cures arises that class of case in which following on some unusual exertion, a scrotal hernia suddenly develops in a young adult.

Age at which Spontaneous Disappearance Occurred. As far as could be ascertained the inguinal herniæ disappeared usually before the age of one year, but in some the hernia recurred at intervals up to the age of three years.

Varieties of Inguinal Herniæ. In the total number of 773 cases of simple inguinal hernia, the proportions were :—right, 477 or 62% ; left, 155 or 20% ; double, 141 or 18%.

In females, the preponderance of the right-sided variety is not so marked, the proportions being :—right, 35 cases or 45% ; left, 27 cases or 35% ; double, 15 or 20%.

The disappearance rate in the three varieties is remarkably constant, being right 24% ; left 25% ; double 23% ; which gives the average figure 24% mentioned above. It will thus be seen that no one variety of inguinal hernia is more prone to disappear than another.

Strangulated Herniæ. Of the in-patient operation returns for these five years the total of herniæ designated strangulated was eight, but in none of these was resection of bowel necessary. These cases were all under two years of age, the youngest being nine months old.

Femoral Hernia. No case of femoral hernia was found. As our investigation was confined to children of three and under, it was unlikely that such a variety would be found, since of five cases occurring in the hospital records during these five years, the youngest was five years of age and it is doubtful if this form of hernia can be considered a congenital manifestation.

Umbilical Hernia. Of the 1018 cases investigated 214 were simple umbilical herniæ. Of these 214 cases there were 112 males (53%) and 102 females (47%). Umbilical, in contrast with inguinal hernia, appears therefore to be about equal in the two sexes.

Incidence of Spontaneous Cure of Umbilical Hernia. Of these 214 cases, 46 were operated upon, 101 disappeared spontaneously and 67 were for one reason or another not operated upon. This implies that half the cases suffering from umbilical hernia are cured spontaneously and do not require operation, under the age of 12 years. The sex incidence of the disappearance rate, was roughly equal in the two sexes.

In a large proportion of those cases in which the umbilical hernia still existed it was claimed that the hernia had become much smaller.

Combined Umbilical and Inguinal Herniæ. Of the 1018 cases there was a combined umbilical and inguinal hernia in 31 cases. Of these, 30 were in males and one in a female.

Incidence of Spontaneous Cure of Combined Umbilical and Inguinal Herniæ. Of the 31 cases there was a spontaneous disappearance of both herniæ in 10 cases, or one-third, and the remainder were operated upon successfully.

Discussion.

There seems to be a general agreement as to the sex incidence in hernia, but on various other points there is a wide discrepancy of opinion and fact.

Inguinal Hernia. Fraser[1] states that of 1000 cases investigated, 906 (90%) were males, and 94 (10%) were females. Of these 1000 cases, 619, (62%) were of the right inguinal, 244 (24%), of the left inguinal, and 107, (11%) of the double inguinal variety, while (30 3%) were not named. He suggests that the explanation of the greater proportion of right than of left

herniæ would appear to be that the right processus vaginalis closes at a slightly later date than the left. Regarding the time for operation he thinks that operation should be undertaken

(1) between the third and sixth months; or
(2) at the end of the second year; or
(3) immediately before the child goes to school;

and that a circumcision should be done before the operation takes place if phimosis is present. Fraser further ventures the sweeping statement that no hope need be entertained of a natural cure after the age of three months.

Examining our figures, we make the total proportion of the incidence of herniæ in males and females as four to one. Fraser (p. 768) states that the proportional incidence of herniæ in males and females is about 20 to 1. Of English authors, McAdam Eccles[2] and Hutchison[3] give the proportions as 5 to 1 which agree with our figures. Kerley[4] makes general statements which bear out our results, but does not quote actual figures. Richter[5], quoting Macready[6], states that "of each 1000 persons ruptured, 175 are affected in the first year of their life," and quoting Coley[7] he says that "the ratio between the sexes is 75% males and 25% females for all types of herniæ." This agrees closely with our figures. He also quotes Ochsner[8] as stating that "in 73% of all children suffering from herniæ from birth to the 6th year, the herniæ must have disappeared before the age of 13."

It will be seen that the figures quoted by Pybus[9] agree closely with our own. He says that in inguinal herniæ 89% are males and 11% females, that it is commonest on the right side (59%), 26% being on the left side and 15% bilateral. He considers that operation should take place any time after six months of age.

The treatment of inguinal hernia at the Hospital for Sick Children is generally:—

1. *Circumcision* in all cases if there is any straining.
2. *Application of a truss* preferably of rubber, as a skein of wool is useless except in plump children with a bubonocele.
3. *Operation after the age of* 1 *year* as then shock, both surgical and anæsthetic, is better withstood and the child has cleaner habits.

While this is the routine treatment, it would seem from the above figures that too pessimistic a prognosis of cure should not be given if operation is refused.

Umbilical Hernia. Regarding umbilical hernia, Fraser[1] carefully differentiates between the uncommon congenital umbilical hernia and the common post-natal umbilical hernia. In the congenital type the contents of the peritoneum tend to herniate through the abdominal wall behind the prolapsed umbilical cord. He does not state the sex incidence in such cases. He debates the best treatment, and is of opinion that if occlusion can be guaranteed for a period of from 4 to 6 months, there is every prospect of a natural cure. He thinks that operation should not be performed upon children below the age of three years.

Kerley[4] states that "of 2000 operations for hernia under 14 years of age at the Hospital for the Ruptured and Crippled only 1·3% were for umbilical herniæ."

Holt[10] advises strapping for umbilical hernia and states that operation above the age of 7 years is rarely necessary.

Conclusions.

We would conclude therefore :—

1. That the incidence of hernia among the out-patients attending a children's hospital is below 1%.
2. That the sex incidence of all herniæ in children is at the rate of 4 males to each female.
3. That inguinal hernia is about four times as common as umbilical hernia, its sex incidence being 9 males to each female.
4. That the tendency to an apparent spontaneous cure is marked. In inguinal hernia a fourth of all cases apparently cure themselves. This tendency to spontaneous cure is higher in females (37%) than in males (22%).
5. That right inguinal hernia is present in 62%, left in 20%, and double in 18%.
6. The sex incidence in umbilical hernia is equal, and about half the cases are cured spontaneously under the age of 12.

For permission to investigate these cases our thanks are due to the Surgeons of The Hospital for Sick Children.

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PERIOSTITIS OF THE METATARSUS.

BY

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Several descriptions have been published during the last few years of affections of the metatarsus. These affections have been given various names, such as " marching fractures," " acute metatarsal overstrain " and " chronic œdema of the feet." They are alike in that apparently healthy people have been affected without any definite cause, and the descriptions give the impression that in spite of different titles they all apply to one and the same condition in different stages.

It is thought that the following notes of three cases may be of interest, because they record the whole course of the disease from the beginning of the first symptoms to their complete disappearance.

All the patients were schoolboys and the trouble began without any history of injury or other obvious cause, although, of course, life at school naturally lends itself to minor injuries at football and other games.

In all three cases the first complaint was of pain in the dorsum of the foot, accompanied by a little swelling and tenderness over the middle of the metatarsal region. At this stage skiagrams showed nothing abnormal but a faint shadow round the middle of the shaft of a metatarsal bone, so faint that it was completely over-looked in one instance at any rate. The shadow became more marked as time went on, and after a month or so films showed a fracture with considerable callus. After another two or three months nothing more than a slight thickening of the bone was visible.

In one case the disease affected two metatarsals one after the other, the second bone being affected while the foot was being rested on account of the first. In the case of this bone at any rate there was no possibility of injury.

Case Records.

Case 1. A particularly well made and healthy schoolboy, aged 14, on June 28th, 1921, complained of pain in the left foot. The dorsum of the foot was a little swollen and tender on pressure over the middle of the second metatarsal. An X-ray film showed a sheath of periosteal new bone round the middle of the shaft of the second metatarsal, without any rarefaction or expansion of the shaft. He was seen by Mr. Harold Wilson, who put the foot in plaster, and he returned to ordinary school life in the following September. He has had no symptoms since in spite of playing hard at all games, and a film in June, 1926, showed a perfectly normal foot.

Case 2. A schoolboy, aged 15, apparently perfectly healthy, on November 28th, 1925, complained of pain in the right foot. There was slight swelling and tenderness as in case 1. A skiagram showed a faint shadow round the shaft of the second metatarsal (Fig. 1). On December 27th, the appearance was that of a fracture with considerable callus (Fig. 2). The appearance on February 10th, after resting the foot is shown in Fig. 3. Since then the boy has lived an ordinary life and has had no recurrence.

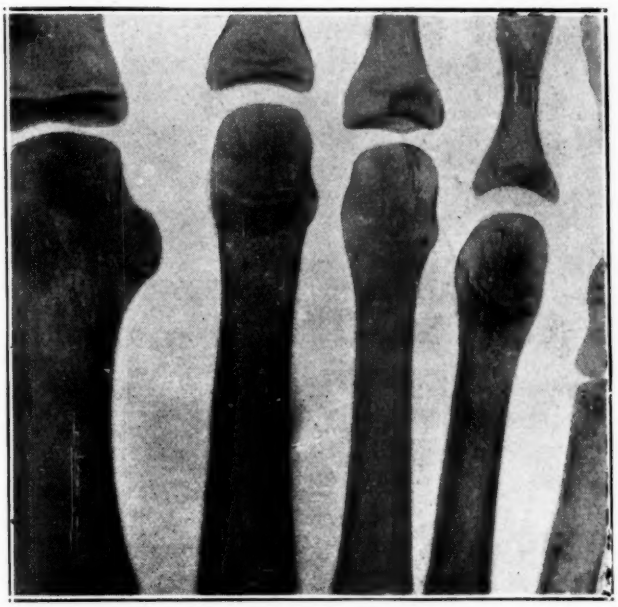

Fig. 1.—Case II., (1/12/25); showing a faint shadow round the shaft of the second metatarsal bone.

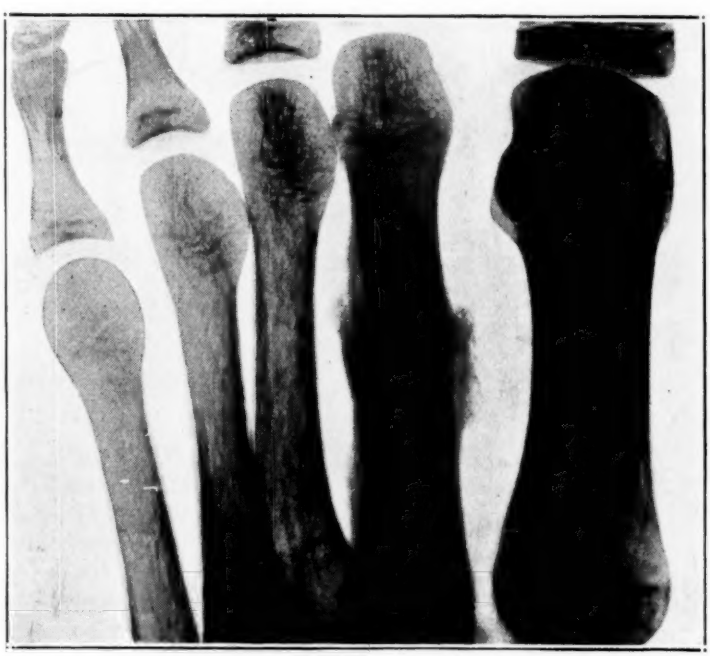

Fig. 2.—Case II. (27/12/25); showing a fracture, with considerable callus, of the second metatarsal bone.

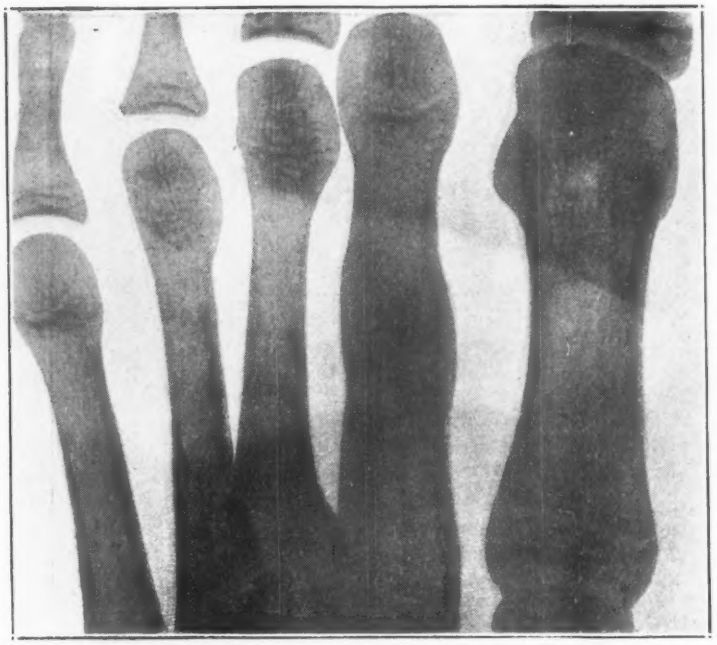

Fig. 3.—Case III. (10/2/26); showing recovery after rest.

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Fig. 4.—Case III., (29/3/26); showing a faint shadow round the middle of the shaft of the third metatarsal bone.

Fig. 5.—Case III., (9/5/26); showing further change in the shaft of the third metatarsal, and a faint shadow round the neck of the fourth metatarsal bone.

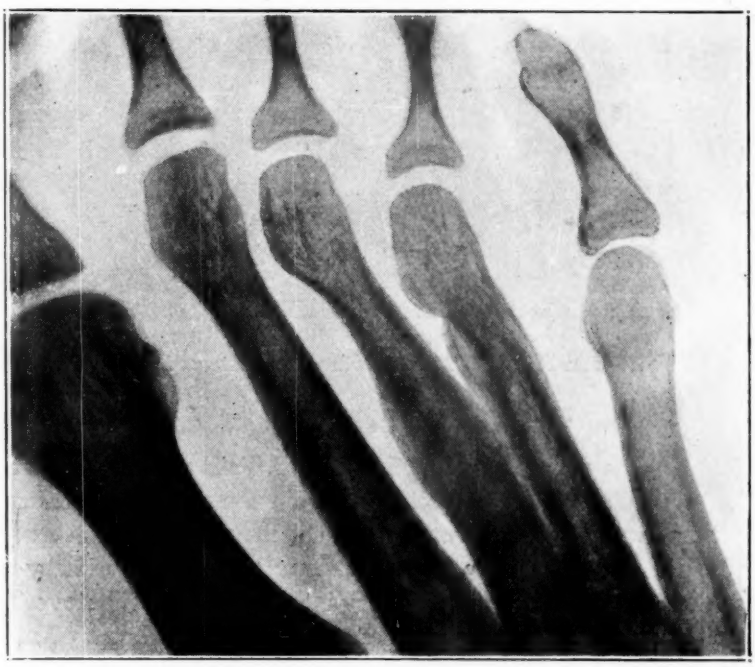

Fig. 6.—Case III., (21/6/26); showing diminution in the callus round the shaft of the third metatarsal, and thickening round the neck of the fourth metatarsal bone.

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Case 3. A schoolboy, aged 17, on March 29th, 1926, complained of pain in the right foot. He was very fat (weight, 14 stones; height, 6 ft.), and his appearance and late development at one time had aroused a suspicion of Fröhlich's syndrome. With the previous two cases in mind, a skiagram (Fig. 4) was taken. This was passed as normal though now, in the light of after events, a faint shadow is visible round the middle of the shaft of the third metatarsal. He went home for the holidays, and danced and played games in spite of the pain which persisted. On his return to school on May 9th, another skiagram (Fig. 5) was taken. The alteration in the shaft of the third metatarsal was now very obvious, and there was also visible a faint shadow round the neck of the fourth metatarsal, though no importance was attached to it at the time. The foot was rested. At a third examination on June 21st, (Fig. 6), there was seen a definite thickening round the neck of the fourth metatarsal, while the callus round the third had become smaller and spindle-shaped. Fig. VII, taken on September 3rd, shows a further stage of recovery. The boy is now—December, 1926—quite free from symptoms and is developing well.

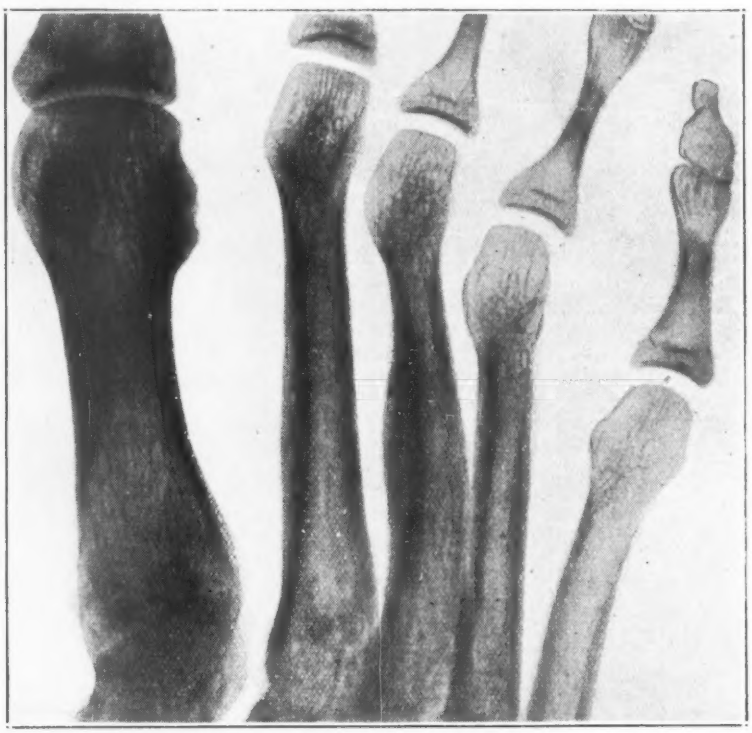

Fig. 7.—Case III., (3/9/27): showing further stages in recovery.

Discussion.

The last two cases were seen by Mr. H. A. T. Fairbank, and were treated in conjunction with him. He was quite sure from the clinical condition and the films that there was a definite fracture of the metatarsal in both patients.

But it is difficult to be sure whether the fracture was the primary condition or whether there was not some preliminary inflammation. Whatever the cause of the condition may be it seems clear that the old hypotheses of mechanical strain, such as marching with a heavy pack, will not altogether account for the

sequence of events. All the patients with the exception of the last, were ordinary healthy schoolboys without any marked valgus or other foot affections. Case II had no valgus at all. Case III had slight flattening of the affected foot, but the arch of the other was unusually high. They were all living and playing games as others in the school. The middle of the shaft of the bone, too, was affected and not the neck, where, as A. H. Pirie in his paper on this subject points out, these bones have to bear the greatest breaking strain. There must be some underlying condition which predisposes to the initial periostitis.

The idea of a periostitis after a hæmogenic infection, such as is suggested by Gosta Runstrom, has little to recommend it in these healthy boys, at any rate less than the other suggestion of a nutritional disorder accompanied by a decreased elasticity of the bones.

In Case III noted above, there was certainly some nutritional disturbance causing the adiposity and late development, and some of the X-Ray films show a definite thinning of the bones in this patient.

Conclusions.

1. There is an affection of the metatarsal bones which can arise in apparently healthy boys of school age without any definite injury.
2. It is a condition which may be easily overlooked, even with an X-ray film, in its early stage.
3. If untreated it can progress until a more or less spontaneous fracture occurs.
4. It begins as a periostitis, and the bone affection, rarefaction and fracture are secondary occurrences.
5. No satisfactory explanation of the cause of the initial periostitis has yet been given.

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FÆCAL FAT ANALYSES IN CHILDREN.

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In a children's hospital the chemical pathologist is often asked to estimate the fat content of fæces. There are several points of importance both in the making of such analyses and in their interpretation. The object of this paper is to collect these points from the literature, and, in illustration of certain of them, to report a number of recent analyses made at the Hospital for Sick Children.

TECHNICAL CONSIDERATIONS.

The term 'fat' in this connection is loosely applied. An estimation of 'total fat' includes all substances soluble in ether, together with the fatty acids liberated from soaps by acid. The substances soluble in ether include neutral fat (the triglycerides of oleic, palmitic, and stearic acids), free fatty acids (oleic, palmitic, and stearic), sterols, pigments, and minute amounts of other substances that need not be considered. 'Split fat' includes preformed fatty acids and fatty acids liberated from soaps. 'Unsplit fat' includes neutral fats, sterols, pigments, etc., and is calculated from the difference between the total and the split fat. It will therefore include any liquid paraffin or other neutral oily matter which may travel through into the fæces after oral administration. It is essential that liquid paraffin be avoided for 3 or 4 days before the collection of the fæces for fat analysis.

Analyses may be made on the moist fresh fæces ([9, 10, 12, and 4]), or on the dried fæces ([1, 3, 7, 8, and 10]). In the former case the ratio of the wet weight to the dry weight must be determined separately, so that the results may be expressed in terms of the dry weight. It would be useless to express the results in terms of the moist fresh fæces owing to the great variation in

water content (diarrhœa, etc.). Each method has its protagonists, but the majority of workers prefer to dry the fæces.

For routine clinical work the method of Holt, Courtney, and Fales [7] is recommended. For special investigations extraction in a Soxhlet apparatus is advised. The soaps should be hydrolysed with aqueous hydrochloric acid, and the resultant mixture, after digestion and concentration, should be taken up with anhydrous sodium sulphate or plaster of Paris (see below). For details of the different methods available the reader is referred to the references given above. A few special points only will be noted here. In clinical work it is a common practice to heat the fæces on a boiling water-bath until it is possible to reduce them to a powder. This takes from a few hours to one or two days. This powder is of course not strictly dry. It is necessary to place it in a desiccator for several days to take it to constant weight. This desiccation is frequently omitted because the clinician cannot afford to wait so long for the analysis. An error of 3 to 10 per cent. is thereby introduced [5].

Hydrolysis of the soaps with acid must not be performed in the presence of alcohol if the fatty acids are subsequently to be determined by titration with alkali, because esterification may occur and introduce a serious error [5, and 4]. The soaps may be hydrolysed with an *aqueous* solution of acid as in the method of Holt, Courtney, and Fales [7]. Cammidge's method in which hydrolysis by aqueous acid is also employed has been shown to be inaccurate [5, and 4] owing to incomplete extraction. Alternatively the following procedure may be adopted. A known weight of the dried fæces is extracted with ether in a Soxhlet apparatus. The ether removes the neutral fat and the preformed fatty acids. The ether is removed, the weight of the ether extract is determined, and the free fatty acids are titrated in the usual way. The residue in the Soxhlet thimble contains the soaps. This residue is heated with acid alcohol (1 per cent. hydrochloric acid in absolute alcohol), dried thoroughly, replaced in the thimble, and again extracted in the Soxhlet apparatus with ether. The resulting ether extract (after removal of the ether) is weighed; owing to the esterification, it must not be titrated. The acid liberates fatty acids from the soaps. Some of the fatty acid combines with alcohol to yield ethyl esters. The degree of esterification depends mainly on the duration of the heating. What is weighed is a mixture of free fatty acids and their ethyl esters. The maximum error which could be introduced by substitution of the ethyl group for hydrogen is of the order of +10 per cent. This for most clinical purposes may be neglected. In fact the omission of proper desiccation after drying on the water-bath (see above), and the esterification, introduce errors opposite in sign which tend to balance one another approximately.

If aqueous acid is used for hydrolysis of the soaps, the resulting mixture cannot then be taken to dryness (and extracted with ether), because a dark tarry mass results which is difficult or impossible to remove from the dish. Moreover the ether-extract from such a mass is so pigmented that it is impossible to titrate it. But after digestion with the aqueous acid, the mixture may be

taken up with anhydrous sodium sulphate or plaster of Paris, and the resulting powder extracted with ether in a Soxhlet apparatus.

When calculating the split fat from the titration of the fatty acids with alkali, the factor "1 c.c. N/10 alkali corresponds to 0·0268 grm. fatty acid" is recommended [5].

INTERPRETATION OF RESULTS.

Analyses of dried stools merely indicate the percentages of fat present in those stools. Without a knowledge of the exact intake and output of fat, it is impossible to decide how much of the food-fat has been digested and absorbed. Certain deductions, however, can be made: thus when, on an ordinary diet, the percentage of total fat in the fæces is much higher than normal, it is clear that either digestion or absorption or both must have been deficient. In these cases the ratio of split to unsplit fat shows whether digestion or absorption is mainly at fault.

The Normal Findings.

The first point for discussion is what is the normal. Table I is compiled from the extensive data of Holt, Courtney, and Fales [7].

TABLE I.

DIFFERENTIAL ESTIMATION OF FAT IN FÆCES OF NORMAL INFANTS AND CHILDREN.

(Holt, Courtney and Fales.)

Age.	Diet.	Total Fat. Percentage of Dried Fæces. Max.	Min.	Av.	No. of analyses.	Percentage of Fæcal Fat. Split. Max.	Min.	Av.	Unsplit. Max.	Min.	Av.	No. of analyses.
8 days —10 mths.	Breast milk ..	61·1	4·4	34·5	44	92·1	51·7	79·8	48·3*	7·9	20·2	44
2—18 mths.	Cow's milk modifications	82·6†	10·2	34·1	94	97·1	22·7	87·9	77·3‡	2·9	12·1	57
16 mths. —10 yrs.	Milk; or milk, bread and cereal.	45·2	17·7	30·7	10	95·1	69·1	86·0	30·9	4·9	14·0	10
1—7½ yrs.	Mixed ..	39·1§	8·7	18·7	62	89·1	44·0	73·1	56·0‖	10·9	26·9	62

* Next highest 33·2.
† Next highest 56·7.
‡ Next highest 55·1 and 31·7.
§ Next highest 33·7.
‖ Only 9 exceed 34·0.

It will be seen that the normal varies with age and the type of diet. In infants the total fat not uncommonly amounts to 50 per cent. of the dried fæces. After infancy it rarely exceeds one-third.

Of the fæcal fat the percentage which is unsplit rarely exceeds one-third both in infants and children. When interpreting results in pathological work the following generalisation is therefore justified :—*Of the dried fæces not more than one-third should be fat, and of that (fæcal) fat not more than one-third should be unsplit, remembering that in infants even one-half of the dried fæces may be fat.* Some investigators would substitute a 'quarter' for a 'third' in the above generalisation.

In clinical work there is little or no useful information to be gained from separate estimations of free fatty acids and soaps. The ratio of free to combined fatty acids (soaps) depends largely on the reaction of the intestinal contents. The ratio of unsplit to split (i.e., free fatty acids plus soaps) fat is the important point, because it indicates the efficiency of fat digestion, whilst the total fat gives a measure of the efficiency of absorption.

As already mentioned the term 'unsplit fat' includes neutral fats (triglycerides), sterols, pigments, and minute amounts of other substances which need not be considered. The weight of the pigments is so small that it can be disregarded. In 12 normal adults Fowweather [4] obtained the following results for the unsaponifiable matter (which consists mainly of sterols) :— 0·64 to 3·88 per cent. of the dried fæces, or 7·8 to 33·3 per cent. of the unsplit fat. For most clinical purposes therefore the quantity of sterols need not be determined.

In all the above analyses what has been determined is the percentage composition, the concentration of the fats, in the sample of fæces analysed. It is important to bear this in mind when interpreting results, otherwise misleading deductions may occasionally be made. The position is somewhat similar to the consideration of sugar analyses in urine. The sugar percentage, for instance, might rise and yet at the same time the day's output might fall owing to the occurrence of oliguria. In the same way the concentration of fæcal fat might appear slightly high, and yet the day's output be low, owing to the total daily weight of dried fæces being low.

Another similar point arises in connection with the percentage of the fæcal fat which is split or unsplit respectively. The following is typical of cases on *low* fat diets with normal digestion and fat absorption :—

(*a*) Expressed as percentage of dried fæces.

	(i)	(ii)
Split fat	6·4	6·26
Unsplit fat	3·9	3·44
Total fat	10·3	9·70

(*b*) Expressed as percentage of the fæcal fat :—

	(i)	(ii)
Split	62·1	64·5
Unsplit	37·9	35·5

The figures in (*a*) are obviously normal, but in (*b*), at first sight, the unsplit fat might appear slightly raised. The figures in (*b*) must, however, be interpreted in the light of the results in (*a*). When the fat in the diet is low the split fat tends to be almost completely absorbed. The unsplit fat, however, corresponds more or less to 'starvation' fæcal fat (6, 2). The exact significance of the latter is not entirely settled, but for our present purposes it may be regarded as fatty matter (including sterols) which has either been excreted into the large intestine, or has been formed by the degeneration of epithelial cells, or has been derived from the bodies of bacteria, etc. In other words a proportion of the unsplit fat is not a residue of the food taken in the diet. When the fat intake is very small this non-food fatty residue may form a high percentage of the fæcal fat.

Pathological Findings.

Fæcal fat percentages give a rough indication of the efficiency of the digestion and absorption of fat. By themselves such estimations are seldom, if ever, pathognomonic of any one disease.

Table II for instance has been compiled from results obtained at the Hospital for Sick Children, for the most part in cases originally suspected of having cœliac disease. All determinations were made by the method of Holt, Courtney, and Fales (7). The cases have been classified into groups according to the final diagnosis made in each instance.

Cœliac Disease.—It will be seen at once that there are no figures peculiar to, or pathognomonic of, cœliac disease. In this disease, when untreated, the rule is to find the total fat percentage abnormally high, but the splitting normal. Conversely, such a chemical finding is a point in favour of cœliac disease if the clinical evidence points to that diagnosis, but the chemical analysis must always be viewed as an extension of the clinical examination. On the other hand, if, in an untreated patient, the total fæcal fat is within normal limits, it is most unlikely that the case is one of cœliac disease. (For a fuller discussion of this condition, the reader is referred to the papers of Miller et al. (11)).

Other abnormal conditions.—The findings of Holt, Courtney, and Fales (7) in various abnormal conditions are summarized in Table III, since they include disorders of which there is no example in Table II, and also illustrate the point that various conditions may give rise to stools with a fat content similar to that in typical cœliac disease.

TABLE II.

FÆCAL ANALYSES AT THE HOSPITAL FOR SICK CHILDREN.

Diagnosis.	Case.	Sex & Age (years).		Percentage of dried fæces as Total fat.	Split fat.	Un-split fat.	Percentage of fæcal fat which is Split.	Un-split.	Remarks.
Coeliac disease	C.A.	M.	1½	58·95	52·05	6·90	88·3	11·7	
„	E.R.	F.	3½	52·85	34·80	18·05	65·8	34·2	
„	E.B.	F.	3	50·75	43·65	7·10	86·0	14·0	
				41·17	37·36	3·81	90·75	9·25	After 1 month's treatment. Serum Ca. 8·3 mgm.
				36·55	31·85	4·70	87·1	12·9	1 week later.
„	M.B.	F.	1¾	47·60	39·95	7·65	83·9	16·1	Serum Ca. 11 mgm.
„	A.M.	F.	1⅙	44·9	33·1	11·8	73·7	26·3	Serum Ca. 11·5 mgm. Bld Cholesterol: 141 mgm.
„	O.W.	F.	1¾	43·8	36·8	7·0	81·7	17·3	
„	A.G.	M.	1⅔	42·00	35·85	6·15	85·4	14·6	Serum Ca. 11·5 mgm. Bld Cholesterol: 137 mgm.
„	B.C.	F.	2	41·2	34·4	6·8	83·5	16·5	
„	B.W.	M.	2	41·2	25·7	15·5	62·4	37·6	
„	A.R.	F.	3¼	39·9	29·9	10·0	74·9	25·1	
Genu valgum. Old coeliac case.	P.M.	M.	11½	33·40	25·05	8·35	75·0	25·0	
Pancreatic infantilism.	F.W.	M.	7	50·6	39·8	10·8	76·6	21·4	Blood sugar: 440 mgm.
				48·20	35·55	12·65	74·0	26·0	After 1 month's treatment.
Chronic indigestion	C.H.	M.	4⅔	53·76	44·12	9·64	82·05	17·95	
				46·1	39·3	6·8	85·2	14·8	12 days later.
„	M.B.	F.	½	23·7	19·9	3·8	84·0	16·0	
„	A.H.	M.	1	23·45	13·60	9·85	58·0	42·0	
„	G.W.	M.	2⅔	18·19	14·35	3·84	78·9	21·1	
„	L.M.	F.	1¼	10·3	6·4	3·9	62·1	37·9	
Chronic diarrhœa.	A.P.	F.	7/12	39·05	33·7	5·35	86·5	13·5	Serum Ca. 11·9 mgm. B. Cholest. 117 mgm.

TABLE II—*continued.*

FÆCAL ANALYSES AT THE HOSPITAL FOR SICK CHILDREN—*continued.*

Diagnosis.	Case.	Sex & Age (years).		Percentage of dried fæces as Total fat.	Split fat.	Un-split fat.	Percentage of fæcal fat which is Split.	Un-split.	Remarks.
Gastro-enteritis.	S.J.	M.	½	60·8	53·5	7·3	88·0	12·0	
,,	J.D.	M.	½	55·20	49·54	5·66	89·7	10·3	
,,	W.D.	M.	5/12	27·5	17·5	10·0	63·7	36·3	
Tetany (gastric)	J.C.	F.	2⅙	47·7	42·0	5·7	88·1	11·9	
Tuberculous peritonitis and meningeal tuberculomata	C.B.	M.	1⅓	61·65	51·60	10·05	83·7	16·3	Autopsy.
Tuberculosis of caecum.	T.H.	M.	6	51·21	34·76	16·45	67·9	32·1	Operation.
Abdominal tuberculosis.	H.H.	F.	5	47·4	21·9	25·5	46·2	53·8	
				18·8	16·9	1·9	89·9	10·1	After 3 weeks on fat-free diet.
Mediastinal tuberculosis	J.B.	F.	7/12	29·65	13·95	15·70	43·7	56·3	
Marasmus.	J.R.	M.	1	22·1	15·4	6·7	69·7	30·3	
Chronic tonsillitis: malnutrition.	W.K.	M.	4⅙	8·29	6·03	2·26	72·7	27·3	
Debility.	E.S.	F.	8⅓	24·4	22·2	2·2	91·0	9·0	
Acetonæmia.	R.M.	M.	17/12	30·45	25·68	4·77	83·4	16·6	
Congenital heart disease and broncho-pneumonia.	L.L.	M.	1¾	34·1	27·05	7·05	79·3	20·7	
Multiple tics.	B.B.	F.	6	9·8	6·85	2·95	69·9	30·1	

It will be seen (Table III) that *diarrhœa* alone in some cases may cause deficient splitting and deficient absorption of fats. Even normal children when passing abnormal stools (Table III) may show a high proportion of unsplit fat, though it should be noted that in no case is the total fat definitely abnormal. In the majority of cases of *rickets* (Table III) the anaylses lie within normal

TABLE III.

PATHOLOGICAL CONDITIONS.

(HOLT, COURTNEY AND FALES.)

Disease.	Age.	Diet.	Total Fat. Percentage of Dried Fæces. Max.	Min.	Av.	No. of analyses.	Percentage of Fæcal Fat. Split. Max.	Min.	Av.	Unsplit. Max.	Min.	Av.	No. of analyses.
Ileo-colitis: Scurvy	8 months	Breast milk ..	—	—	57·1	1	—	—	67·3	—	—	32·7	1
Diarrhœa	6 months	,, ,, ..	—	—	53·7	1	—	—	56·2	—	—	43·8	1
,, ...	5 months	,, ,, ..	—	—	17·2	1	—	—	—	—	—	—	—
Syphilis. Ill after salvarsan.	7 months	,, ,, ..	—	—	17·0	1	—	—	71·9	—	—	28·1	1
Diarrhœa	2½ mths. to 14 mths.	Modifications of cow's milk.	61·4	3·9	35·1	34	63·0	17·5	46·4	82·5	37·0	53·6	9
Abnormal stools* ..	16 mths. to 7 years	Modifications of cow's milk.	34·3	4·3	15·1	19	89·2	18·6	64·1	81·4	10·8	35·9	19
Rickets	17 mths. to 4 years 4 mths.	Mixed	50·7†	14·8	29·0	16	85·3	70·7	78·7	29·3	14·7	21·3	14
Intestinal indigestion	2 years 1 mth. to 9 years 4 mths.	Mixed	60·5	19·5	35·1	21	91·1	60·4	80·7	39·6‡	8·9	19·3	21

* Normal children but with stools which were abnormal—*i.e.*, very acid, or showing considerable mucus, or containing undigested food, etc.

† Only 4 above 33.

‡ Next highest 34·2.

limits. In many of the cases of *chronic intestinal indigestion* (Tables III and II) the results are exactly similar to those obtained in typical cœliac disease (Table II)—total fat in excess, splitting normal. In *gastro-enteritis* (Table II) the results are within normal limits, taking into consideration the ages of the patients. The figures in *tuberculous peritonitis* (Table II) show the same deviation from the normal as in cœliac disease. Clinically, it is not uncommon for some children suffering from tuberculous peritonitis to become intolerant of fat, and unless the amount of fat in their diet is restricted their stools become large, pale, and fatty ; it is probable that the high fat content of the fæces is due to obstruction to the lacteals. The rapid fall in case H.H. after three weeks on a fat-free diet supports this hypothesis.

Fat retention.

Fat retention investigations are elaborate and time-consuming. In clinical work therefore they are reserved for special cases. None the less brief mention of them is necessary. The patient is placed on an accurately measured diet. The fat content thereof is calculated with the aid of tables, or better by analysis of samples of the food used for the diet. After a preliminary period of three or four days on this diet a 'marker' (usually carmine or charcoal) is administered. The fæces are collected from the appearance of this marker until the appearance of a second marker which is given after several days at the same hour as before. The fæces coloured by the first, but not those coloured by the second marker are included. The food given after the first and before the second marker constitutes the diet of the metabolism period. In the case of infants and young children a metabolism bed must be employed for collecting the stools. The metabolism period should not be less than three whole days. More accurate results are obtained by using longer periods—up to seven days. Obviously the whole of the stools must be collected. This is not difficult with a specially trained nursing staff, but is often not easy in a training school. As soon as a stool has been passed it is either stored in a refrigerator, or is at once sent to the laboratory to be dried. The total dried fæces of the whole period is weighed, and samples are taken for analysis. The output of fat and the percentage retention is calculated.

The findings of Holt, Courtney, and Faies (5) for normal and abnormal children, and our own results in two cases of cœliac disease (four-day metabolism periods) are given in Table IV.

In normal infants over 90 per cent. of the ingested fat is retained when they are breast-fed. On modifications of cow's milk, fat retention is not quite so good, but in most cases it exceeds 70 per cent. In older children on mixed diets it generally exceeds 90 per cent.

In rickets fat retention is generally normal. Simple diarrhœa often reduces the quantity of fat retained, in some instances considerably. In chronic intestinal indigestion there is frequently a considerable loss of fat in the fæces. In fact, so far as analytical data are concerned, there is no difference between typical cœliac cases and some of the more severe examples of chronic intestinal indigestion.

TABLE IV.

FAT RETENTION.

Condition.	Age.		Diet.	Fat Intake, gm. daily.		Fat Output, gm. daily.		Fat Retention, per cent.			No. of Observations.
	Max.	Min.		Max.	Min.	Max.	Min.	Max.	Min.	Av.	
Normal	10 mths.	3 weeks	Breast milk ..	42·5	9·8	2·26	0·27	99·2	90·3	95·1	8
Diarrhœa	5½ months		,, ,, ..	7·0		1·48		—	—	79·0	1
Ileocolitis	8 months		,, ,, ..	15·7		5·71		—	—	62·6	1
Acute Diarrhœa ..	**6 months**		**,, ,,** ..	**25·2**		**12·00**		—	—	**52·5**	1
Normal	18 mths.	2 mths	Modifications of cow's milk.	48·3	11·4	7·57	0·38	97·4	71·9	88·6	67
Diarrhœa	14 mths.	2½ mths.	,, ,,	39·7	11·6	14·54	1·77	19·1	12·9	74·3	29
Normal	10 years	1 year	Mixed	61·0	21·8	5·65	0·71	98·0	86·3	93·7	78
Rickets	4 years 4 mths.	1 year 5 mths.	,, ...	61·0	19·6	8·59	1·49	97·3	78·4	91·6	16
Intestinal indigestion.	9 years 4 mths.	2 years 1 mth.	,, ...	74·2	12·7	18·67	1·95	91·1	26·5	78·4	21
Coeliac	1 year	9 mths.	Mixed	10·33		6·63		—	—	**35·8**	1
Coeliac	3 years		,, ...	13·06		2·94		—	—	77·5	1

SUMMARY.

(1) A number of technical points in the differential estimation of fats in fæces are discussed.

(2) The findings in normal children of different ages and on various diets are summarized (work of Holt, Courtney, and Fales).

(3) The following generalization is made: normally of the dried fæces not more than one-third should be fat, and of that (fæcal) fat not more than one-third should be unsplit, remembering that in infants even one-half of the dried fæces may consist of fat.

(4) Attention is drawn to various points in the interpretation of results, with special reference to cœliac disease. A series of analyses at the Hospital for Sick Children is given in illustration.

(5) Fat retention experiments and results are discussed briefly.

We wish to thank members of the Staff at the Hospital for Sick Children for permission to investigate their cases, and Miss E. M. Taylor and Mr. R. J. Bromfield for their technical assistance.

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SCLEREMA NEONATORUM AND ITS RELATION TO FAT NECROSIS.

REPORT OF A CASE BY

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Sclerema neonatorum is a rare disease of early infancy, characterized by swellings in the subcutaneous fat, of characteristic distribution—on the back, shoulders, buttocks, and cheeks. In these lesions the fat crystallizes out during life, probably as neutral fat, and in well-marked cases the crystals give rise to an inflammatory reaction of the "foreign body" type, with giant cells. In these cases also, calcium is deposited in the lesions.

The histological and chemical work described in this paper was undertaken by one of us (F.K.H.) at the suggestion of Dr. G. A. Harrison, and is on the same lines as his own investigations on sclerema neonatorum [1] [2].

I. CLINICAL RECORD (G.L.S.K.).

An infant girl, aged 2 weeks, was admitted to Paddington Green Children's Hospital, under Dr. Sutherland's care, suffering from frequent convulsions. The child had been born at full term by an instrumental labour, had been partially asphyxiated at birth, and had weighed 8 lbs. It had been given the breast for the first 3 days, and later Allenbury's Food, but had never taken the feeds well. A red rash had appeared at the age of 9 days, and had gradually spread over the body.

There was nothing abnormal in the family history.

On examination the infant was small and poorly nourished. Convulsions were taking place about every half hour, the arms, legs, and face showing clonic contractions. The fits were chiefly right-sided, and the right leg was somewhat spastic. The knee jerks were equal and active; the neck muscles were not rigid; the pupils were equal, but reacted sluggishly to light, and there was no strabismus. A dark red morbilliform eruption was present on the trunk, limbs, and face. There were petechiæ on the back, and in the mucous membrane of the hard palate. There was considerable peeling of the skin around the mouth, and the nails of the fingers and toes, but practically none on the palms of the hands.

Over considerable areas the skin and subcutaneous tissues were indurated, and of uneven surface on palpation. The skin could not be pinched up over these areas, but the subcutaneous tissue was freely movable on the deeper structures. The induration was present over the greater part of the dorsum of the thorax, and the skin over this area was purplish in colour, and the capillary circulation poor. There was a cyst of about ¾-in. in diameter near the inferior angle of the right scapula. Other indurated areas were present over both deltoids, the lateral and proximal portions of the thighs, and on both buttocks, where the induration seemed to be deeper seated, and where there was ulceration of the overlying skin. There was also an area of induration of about 1-in. in diameter over the right zygoma; this area was umbilicated, and shewed central softening, and, like the other nodules, was movable on the deeper structures. The distal segments of the limbs were free from induration, except for a few nodules over the extensor surface of the right forearm.

The lower border of the liver could be felt in the right nipple line at the umbilical plane, but it could easily be displaced to the subcostal plane by pressure. The gall bladder was easily palpable, and very tense. The spleen could not be felt.

While the infant was in hospital her condition fluctuated considerably. The temperature varied between 96° and 101.2°. For the greater part of the time the temperature was raised or normal. On 6 occasions only it fell as low as 96° F. Three days after admission the convulsions had ceased and the rash had disappeared; the petechiæ increased in number before finally vanishing. The child died 21 days after admission. Vomiting occurred during the last 5 days. The Wassermann reaction was negative. A radiological examination was made post mortem, and shewed no opacities in the subcutaneous tissues, but this may have been due to the use of too hard a ray.

Post Mortem Examination. Weight, 6 lb. 4 oz. There was fine desquamation of the skin over the whole body, and especially on the back.

The firm, indurated nodules in the subcutaneous tissue have already been described. In these areas the fat had the appearance of lard and was of firm consistency. Elsewhere the subcutaneous fat was small in amount. The cyst near the inferior angle of the scapula contained a small quantity of thick creamy material, which microscopically shewed a few tufts of acicular crystals. There was another small cyst, the size of a pea, in the indurated tissue over the left deltoid. The perinephric fat was small in amount but was also white in colour. The liver was slightly enlarged and engorged, and shewed ptosis. The other organs shewed no macroscopic change.

Histological Examination The *pancreas* shewed some post-mortem autolysis, but no pathological change. In the *liver* there was marked engorgement of the sinusoids. The parenchyma cells shewed cloudy swelling, and in places fatty degeneration. The *kidneys* shewed moderate hyperæmia. Hyaline thrombi were present in the glomeruli, which were adherent to the Bowman's capsules. There was an exudate of serum into the Bowman's capsules of some glomeruli. The tubular epithelium shewed marked degeneration, with vacuolation. In the *suprarenals* there was marked hyperæmia of the deeper layers of the cortex.

I wish to express my thanks to Dr. G. A. Sutherland for allowing me to publish this case.

II. HISTOLOGICAL AND CHEMICAL EXAMINATION. (F.K.H.).

1. Histology of the Subcutaneous Tissues.

Paraffin sections. There is no pathological change in the cutis. In the subcutaneous tissue, many of the fat cells contain an eosin-staining substance, in which may be seen clefts, left by the solution of crystals. The clefts appear as fine radiating lines, radiating sometimes from a point in the centre of the fat cell, but usually from a point near the periphery. The arrangement of the clefts is exactly similar to the arrangement of the crystals seen in frozen sections. There are no clefts in the interstitial tissue.

No signs of calcification are found. There is some inflammatory reaction but it is not marked. The cells present are all young fibroblasts and mononuclear cells. There are no giant cells.

Frozen sections. The fat globules are filled with tufts of long, anisotropic, acicular crystals, which do not extend outside the fat cells. The contents of the fat cells stain red with Sudan III and pink with Nile blue sulphate. If a section stained by Nile blue is heated on the warm stage until the crystals melt, the pink staining becomes more intense than in the unheated section. The solid crystals themselves are presumably unstained, though, as viewed with the crossed Nicol's prisms, the light passing through them shews the colour of the surrounding stained fat.

The melting point of the crystals, and their solubility in various solvents, have been determined, using the polarising microscope and a warm stage. The crystals melt at 50-56° C. On cooling the section, they begin to reappear at 30° C. There is no liquid crystal formation,

Solubility of the crystals. In *alcoholic soda* (N/2 NaOH) the crystals are insoluble at room temperature, and dissolve at 45° C. In *alcohol* (absolute) the majority of the crystals disappear at 45° and over. All disappear below 60°. In *ether*, if by evaporation of the solvent the section is allowed to cool below room temperature, the crystals do not appear soluble, but they dissolve at once when placed on the warm stage at 25° C. (The actual temperature of the section would no doubt be lower than this, owing to evaporation of the ether.) In *petroleum ether*, the crystals dissolve at once on the warm stage at 25° C. They are also soluble on heating in *acetone* and *benzene*.

Benda's reaction. This is a test for the presence of free fatty acids and soaps. Small pieces of tissue, hardened in formol, are treated with a mixture of copper acetate, acetic acid, and chrome alum. If fatty acids or soaps are present, the copper combines with them to form copper soaps, which form conspicuous green masses visible to the naked eye, and appear in frozen sections as tufts of green acicular anisotropic crystals. The reaction is negative in this case.

Melting point of the crystals in sclerema. The appearance of anisotropic acicular crystals in the fat globules in frozen sections of fatty tissues, and of organs shewing fatty degeneration, is very common. This is of importance, since the appearance of acicular crystals has often been assumed to imply the presence of free fatty acids. This is an unjustifiable assumption: the presence of crystals is not in itself pathological.

It is therefore of interest to compare the melting points of the crystals in normal infants' subcutaneous fat, and in sclerema. This has been done by Harrison [1], who found that the melting point of the crystals in sclerema was higher than that of the normal crystals. He has given me the opportunity of making further observations on his material, using the polarising microscope and warm stage: the results are given in Table I.

TABLE I.

CASE	Crystals melt at:	Crystals reappear at:
Harrison: Case III.		
(1) Short crystals, of general distribution.	31°-34° C.	21° C.
(2) Tufts of long acicular crystals.	Not melted at 60° C.	
Harrison: Case IV.		
All crystals alike.	43°-62° C.	47° C. and under.
Present Case		
All crystals alike.	50°-56° C.	30° C.
Normal Infant (aged 1 wk.)		
Subcutaneous fat.	31°-37° C.	23°-21° C.

In making these observations it is necessary to raise the temperature of the warm stage very gradually, keeping it steady at a given temperature until it is evident that there are crystals present which will not disappear. Even when this is carefully done, the melting points are not sharp; for example, in Case IV, although some crystals began to melt at 43° C., there were others which were not melted when the temperature was steady at 59° C. Yet there

was no sharp distinction between the crystals of the lower and higher melting points. In this case, crystals were present both within and without the fat globules, and, upon the whole, the extracellular crystals had a higher melting point than the intracellular crystals.

In Case III there were two distinct types of crystal. Some were fine short rods with a melting point practically identical with that of the crystals in normal fat. These would not be present during life and are not pathological. Other crystals were present—the long crystals arranged in tufts—with a melting point above 60° C., which was the limit to which the warm stage could be taken. These crystals were certainly present during life, and would account for the inflammatory reaction with giant cells, characteristic of the response to irritation by a foreign body.

The determination of the melting points gives little help in identifying the crystals, but it does serve to distinguish the crystals which were present during life, and to demonstrate the difference between the normal and sclerematous fat. In the case described in this paper, it cannot be definitely said that the crystals were present during life: although they required a temperature of 50°—56° C. to melt them, they did not reappear until cooled to 30° C., and therefore may have been present in the liquid state at body temperature. Nevertheless, there is an abnormality in the fat, since the melting point of the crystals is higher than that of the crystals in normal fat.

The question of saponification. Since a number of cases, apparently identical with sclerema, have been reported as cases of subcutaneous "fat necrosis," it was a point of special interest to determine whether hydrolysis or saponification occurs in sclerema. Harrison[1] [2] considered that there was no appreciable liberation of free fatty acids in his cases, and that certainly the crystals were not fatty acids, but probably neutral fats. This opinion was based (*a*) on the microchemical finding, that the crystals in frozen sections were not soluble in alcoholic soda in the cold, and only disappeared on heating above their melting point: and (*b*) on chemical evidence, that the acid values of the ether extracts of sclerematous tissue, though higher than the normal values, were far lower than would have been expected if the crystals present in the sections had been fatty acid crystals. My own histological and chemical results confirm this view. This histological evidence against saponification is:—(1) failure of the crystals to dissolve in cold alcoholic soda; (2) negative Benda's reaction: and (3) absence of any evidence of soap or free fatty acid in sections stained by Nile blue sulphate even when the crystals are melted.

The case described in this paper seems to be at an earlier stage than those described by Harrison. There are no crystals outside the fat cells, and therefore no "foreign body" reaction, and there is no microscopic evidence of calcification.

2. Chemical Investigation of the present Case.

Methods. The subcutaneous fat from the affected regions was divided into two portions. The first, (A), was cut up into small pieces, spread on a watch-glass, and dried to constant weight in a vacuum dessicator. The second, (B), was cut up and dried by grinding with sand and anhydrous sodium sulphate to form a powdery mixture. Both samples were extracted with ether, for 3 to 4 days, in a Soxhlet apparatus. The ether soluble portion after evaporation of the

ether (the "ether extract") was stored in a vacuum dessicator over $CaCl_2$ and paraffin shavings until constant weight was reached. The ether insoluble portion ("ether-extracted residue") from (A) was similarly stored.

Drying without sodium sulphate is very slow, and much hydrolysis may occur while the tissue is in the dessicator. The ether extract from fat so treated is therefore unsuitable for determinations of the acid value. But since an "ether-extracted residue" free from contamination was required for the determination of calcium and of soaps, the fat had to be divided into two samples as described above. The "ether extract" from (B) was used for the determination of the melting point, acid value, saponification value, and iodine value; the "ether extracted residue" from (A) was used for determinations of calcium and soaps.

Ether extract. The melting point was estimated by the open capillary method; the acid value and saponification values by the usual standard methods, and the iodine value by Wij's method.

Cholesterol was not estimated. The chloroform solution of the fat gave a brown colour with the acetic anhydride and sulphuric acid, which made colorimetric methods (Myers & Wardell) impossible, and there was not enough material available for the digitonin method.

Ether-extracted residue. Total Calcium was estimated in the ash of the tissue by Kramer & Tisdall's method.

Soaps. The soaps of Ca, K, and Na are soluble in amyl alcohol (Maver & Wells, (3)). To determine the amount of calcium present as soap (if any), the ether-extracted residue was extracted with amyl alcohol in a Soxhlet apparatus heated on a sand bath (8 to 9 hours). The amyl alcohol was evaporated to small volume and the solution transferred to a crucible. The remainder of the amyl alcohol was driven off by heating on a sand bath and the residue ashed in a furnace. No ash remained. This excludes sodium and potassium soaps as well as calcium soaps.

The efficiency of the amyl alcohol extraction was checked by testing the method with calcium palmitate, which was extracted completely under the same conditions.

The results are given in Table II.

TABLE II.

	Ether Extract				Ether Extracted Residue	
	Melting point	Acid Value: mgm.KOH per 1 gm. fat	Saponification Value: mgm.KOH per 1 gm. fat	Iodine Value: gm. iodine per 100 gm. fat	Total Calcium: % of residue	Soap
Sclerema	47° C.	2·7	209	46·7	·66%	Absent
Normal	23° to 44·6° C.	0·9 to 2·7	190 to 206	46·7 (average)	·072%	—

The normal figures are here taken from Harrison's paper.(1). Those for the acid value, saponification value, and total calcium are his own figures. The iodine value is an average of very variable figures collected from the literature for children of 1—2 months.* Harrison's series of normal controls does not include a case as young as ours, and it is necessary to compare children of the same age, since the iodine value increases with age.

The figures show no hydrolysis or saponification of the fat: the free fatty acid is not increased and no soap was found.

* The figure given as normal was obtained on the separated fatty acids, and is therefore not really comparable with my figure. The difference in iodine value between the fat and fatty acids would probably not be more than 5%, and would not be sufficient to bring the figure outside normal limits.

There is, as in Harrison's cases, no change in the iodine value, but, as he has pointed out, this does not disprove the theory that the raised melting point of sclerematous fat is due to a diminished proportion of olein, since the olein might be diminished sufficiently to cause a definite rise in the melting point without producing a significant diminution in the iodine value.

It is of interest that the calcium content of the tissue shews a marked rise, without any microscopic evidence of calcification, and in the absence of calcium soaps. The formation of calcium soap is said to be an important stage in many types of calcification—atheroma, Monckeberg's arterio-sclerosis, calcified fibromata, calcified tuberculous nodules, and pancreatic fat necrosis—and is regarded as the earliest stage in the deposition of calcium (Klotz[4] [5]). If sclerema were essentially a "traumatic fat necrosis" associated with saponification, one would expect this method of calcification. Since our case is too early to shew microscopic or radiological evidence of calcification, one cannot lay much stress on the absence of calcium soaps, but there is a marked rise in the calcium content of the tissue without soap formation.

Summary of the results in the present case of sclerema.

(1) Fat cells contain an eosin-staining substance with clefts left by crystals.
(2) There is some inflammatory reaction.
(3) Crystals occur in the frozen sections, of a higher melting point than those in normal fat.
(4) There is no histological evidence of saponification.
(5) There is no histological evidence of calcification.
(6) The fat extracted from the tissues has a raised melting point, but the acid value, saponification value, and iodine value are normal.
(7) The residue after extraction of the fat has a high calcium content, but contains no soap.

III. TRAUMATIC FAT NECROSIS, AND "ADIPONECROSIS SUBCUTANEA NEONATORUM."

No attempt will be made here to summarize the literature on sclerema neonatorum; a review will be found in Harrison's paper[1]. But there are in the literature a number of cases, closely resembling sclerema, and apparently identical with it, described as "traumatic fat necrosis" or "adiponecrosis subcutanea neonatorum."

"Traumatic" or "ischæmic" fat necrosis is a well recognized condition which may occur as a result of injury to fatty tissue. It may occur in any situation, but is commonest in the fat overlying the breast. This remark of course applies only to adults.

Frozen sections of the material shew acicular crystals, and the paraffin sections shew an eosin-staining substance filling some of the fat cells, with radiating crystal-clefts within it. The clefts may also occur in the interstitial tissue. There is a cellular inflammatory reaction, often of the "foreign body" type, with giant cells and "foamy" cells (lipophages). Calcification and fibrosis occur in the late stages.

Cases have been published by Lee and Adair[6], Farr[7], Parsons[8], Lecene and Moulonquet[9] and Hadfield[10]. Evidence of the saponification is given by Farr, and by Lecene and Moulonguet.

Lecene and Moulonguet[9] described several cases, mostly in women, occurring in the fat overlying the breast. They regarded the process as closely similar to pancreatic fat necrosis, and regarded the saponification as the primary lesion, giving rise to a secondary inflammatory reaction. They demonstrated the presence of saponification by Nile blue staining, and they noted that crystals were present in the normal fat, and that the crystals seen in the necrotic areas had a higher melting point than those in the normal fat.

Farr[7] produced experimental fat necrosis in the subcutaneous tissue of pigs by trauma, and demonstrated saponification in these cases by means of Benda's reaction and Nile blue staining. His first case of human "ischæmic fat necrosis" occurred in an infant, and, from the clinical and histological description, seems to have been identical with sclerema. It is not clear whether he used Benda's reaction and Nile blue staining in this case.

Cases identical with sclerema have been described as "subcutaneous fat necrosis of the newborn" or "adiponecrosis subcutanea neonatorum" by Bernheim-Karrer[11], Carol and Van der Zande [12] and others. The case described by Carol and Van der Zande supplies evidence that saponification may occur in these cases. They do not regard their case as one of "sclerema," but there has been much confusion in the terminology of the condition, and their case is evidently one of "sclerema" in the sense in which the term is used in this paper. They reserve the term for a more severe disease, with marked constitutional symptoms. Their case is described as follows :—

A boy, born by a normal but prolonged labour, and asphyxiated at birth, seemed normal until the age of 3 weeks, when a lump developed on the back, between the shoulder blades, and spread over the whole upper part of the back. A week later, similar swellings developed over the left shoulder and in both cheeks, and lastly in the buttocks. These swellings were attached to the skin, but movable on the deeper structures; they were firm, not fluctuating, and not tender. The child died in convulsions at the age of 5 weeks.

Sections of the subcutaneous tissue shewed infiltration with lymphocytes, fibroblasts, and giant cells of the foreign body type. The fat cells and their nuclei stained poorly, and the intercellular partitions were œdematous. Many cells were filled with a granular substance shewing star-shaped crystal-clefts, and these clefts were also present in the connective tissue trabeculæ.

In frozen sections, tufts of anisotropic acicular crystals were seen. Sections stained by Nile blue shewed some fat cells with pink-stained contents, others with light blue contents, others deep blue. The anisotropic crystals were most conspicuous in the pink cells, and there was no double refraction in the deep blue cells. Corresponding cells could be recognised in sections stained by Fischler's method: the cells which were dark blue with Nile blue were blue-black with Fischler's stain. (Fischler's method is a modification of Benda's, and differs in that the fatty acids and soaps are stained blue-black—see Fischler [13] and Klotz [5]).

Carol and Van der Zande regard the presence of double refraction as implying the presence of cholesterol esters. This is not convincing. As far as the *crystals* are concerned, the presence of double refraction means little, for so many crystals shew it. Where double refraction appears to occur diffusely in a fat globule, it is necessary to look closely for crystals, as small crystals densely arranged in a fat cell in a thick section may cause the globule

to shew double refraction, and the crystalline structure may not be very obvious. True liquid crystals of cholesterol esters, as seen in frozen sections in xanthoma, shew a different and very definite appearance—clear cut spherical globules, appearing as "Maltese crosses" under the crossed Nicol's prisms.

This case clearly shews that saponification or hydrolysis of the fat may occur in sclerema neonatorum, although this saponification cannot be the primary event, since it has been absent from Harrison's cases and the case described in this paper.

IV. NON-PANCREATIC FAT NECROSIS.

I have had the opportunity of examining one case, that of an adult male, in which saponification was found in the retroperitoneal fat. For this material I am indebted to Dr. H. A. Lucas.

An irregular mass arising from the retroperitoneal tissue was found incidentally at autopsy, in a man who died of arteriosclerosis of the coronary arteries; there was also a very large right inguinal hernia, but this had no relation to the mass in question, which was attached to the descending colon. There was no perforation of the gut, and it is improbable that the condition was due to an escape of pancreatic lipase. The mass was irregular in shape, and on macroscopic examination shewed fibrosis and small areas of calcification.

Paraffin sections. There is a broad band of formed fibrous tissue on the surface of the mass, and thick fibrous trabeculæ running through it. There is no sign of recent inflammation.

The mass consists of fatty tissue, and there are groups of fat cells which contain a homogeneous hæmatoxylin-staining material; in some cases this "calcification" occupies the whole cell, but in most it occupies the periphery and forms a crescentic or annular mass.

Frozen sections. Unstained sections. Collections of short, rod-like crystals are present in some of the fat cells. Melting point, 35°—42° C. The crystals are soluble in ether, petroleum ether, benzene, and alcohol. They probably consist of neutral fat.

In places there are rounded and gyrate hyaline masses, appearing milky under the crossed Nicol's prisms. These masses are insoluble, even when heated, in ether and petroleum ether, and insoluble in 10% aqueous HCl. In *acid alcohol* (1% HCl in 95% alcohol), they are soluble at once in the cold. With *acid alcohol* (1% HCl in 60% alcohol), the immediate effect is to produce numbers of short, fine, anisotropic crystals, which dissolve when the section is warmed with the acid alcohol.

This suggests that these masses consist of soaps, which would yield fatty acids on treatment with acid alcohol, the fatty acids then dissolving in the alcohol.

Frozen sections stained by Benda's solution, Sudan, and Hæmatoxylin. Some areas shew normal Sudan-stained fat containing a few crystals. Elsewhere there are very well-marked necrotic areas, in which are large, irregular masses consisting of the green, crystalline, doubly-refracting copper salt. In most of these masses the original form of the fat globules is lost; in places the original form is just recognisable by the annular or gyrate arrangement of the crystal masses, as if the contents of neighbouring cells had fused. Occasionally, in the midst of the copper soap, is seen a structureless material, deeply stained with hæmatoxylin,—possibly calcified material.

Around the green crystalline masses are fat cells which retain their structure. Some are filled with a homogeneous material, lightly stained with hæmatoxylin. Others still retain Sudan-stained fat, which usually does not fill them but forms globules or rings in the periphery of the cells.

Frozen sections stained by Benda's solution, Hæmatoxylin, and Eosin. These shew the same features as above, but some cells are seen to be filled with an eosin-staining substance.

Benda's reaction after treatment with alcohol. After removal of the free fatty acid by warming with 95% alcohol, the sections still give Benda's reaction as strongly as before. The reaction, therefore, must be mainly due to soaps.

Nile blue staining. The necrotic areas shew dark blue masses containing short crystals; these masses seem to correspond with the masses of copper crystals in the Benda-stained sections. Elsewhere in the necrotic areas are fat cells filled with a pale blue substance. These seem to correspond with the cells described above as containing material staining with eosin or hæmatoxylin. The normal areas contain pink-stained fat which contains crystals. If the section is heated, the crystals when melted merge with the surrounding material and take on the same colour as the surrounding material, blue or pink as the case may be.

It is difficult to interpret all the staining reactions here seen, but it is clear that the material shews a fat necrosis associated with saponification and calcification, and the appearance of the stained frozen sections is very similar to that described by Carol and Van der Zande in their case of "adiponecrosis subcutanea neonatorum."

Summary and Conclusions.

(*a*) A case of sclerema neonatorum is reported, with observations on the histology and chemistry of the subcutaneous fat. Acicular crystals are present in the subcutaneous tissue, with an abnormally high melting point. These are not fatty acid crystals, but probably neutral fats. There is no hydrolysis of the fat. Chemical observations on the fat extracted by ether confirm the facts of the raised melting point and absence of hydrolysis. The tissue has a raised calcium content in the absence of radiological and microscopic evidence of calcification.

(*b*) A consideration of the literature shews that hydrolysis may occur in sclerema, and this explains the fact that the acid values of the cases reported by Harrison were slightly high. Sclerema neonatorum is thus brought into line with cases of non-pancreatic fat necrosis, although it is clear that in sclerema (as possibly in non-pancreatic fat necrosis) saponification is not the primary lesion.

(*c*) A case of saponification in the retroperitoneal tissue is described for comparison.

I wish to express my thanks to Dr. G. A. Harrison. The work was undertaken at his suggestion and carried out in his laboratories, first at Great Ormond Street, and later at St. Bartholomew's Hospital, and I am indebted to him for suggestions and advice throughout.

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OESOPHAGECTASIA IN A CHILD.

BY

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Dilatation of the œsophagus from cardiospasm is a rare condition in children, and this example is of further interest because for the first time, as far as I know, an acute inflammatory lesion affecting the cells of Auerbach's plexus in the lower end of the œsophagus is shown to be associated with its development.

At death this male child was six years old. Since the age of six months he had suffered from attacks of vomiting which appeared immediately after food. Intervals of ten days to three weeks occurred in which this did not happen, and once for six weeks he was free. For four weeks before admission to hospital he vomited immediately after every kind of food or drink; a few days after admission to hospital he died.

At eight months he had broncho-pneumonia and thereafter developed phthisis for which he was treated in a sanatorium for about a year; when two-and-a-half he had whooping-cough.

Post-Mortem Examination.

A post-mortem examination was made by Dr. Anderson, and the only points of interest in the autopsy protocol were, that a scar of healed phthisis was found in the apex of the left lung, congestion was present in the right base, and calcification of one or two bronchial glands was noted. No evidence of active tuberculosis was seen anywhere. The pyloric and pelvi-rectal areas were of normal size and appearance.

The œsophagus (Fig. 1) was 5¼ in. in length from the cricoid to the cardia and showed a fusiform dilatation measuring 2¼ in. at its greatest circumference: at the cardia the measurement was ½ in. The circular muscle fibres were hypertrophied from the cardia throughout the dilated area, the thickness of the wall being approximately 9/32 of an inch at the cardia, 3/16 at the maximum dilatation 2½ in. above the cardia, and gradually narrowed to normal thickness about 1 in. below the cricoid. Several minute erosions of the mucous membrane were found throughout the affected area.

Microscopic Examination.

Section made just above the cardia showed the epithelial layer to be pitted with numerous erosions, and absent in other parts (Fig. 2). The submucous coat was invaded by masses of lymphocytes and endothelial cells with congestion of vessels, and the muscularis mucosæ was increased in thickness, while hyaline changes in some of the fibres were noticed. There was definite and striking hypertrophy of the circular muscle layer, and here and there clumps of inflammatory cells occupied the interspaces; fibrotic changes in some of the fibres was seen and hyaline and fatty change in others.

In the longitudinal layer, as usually happens in these cases, not much alteration was evident, although here too degenerative changes can be seen and a few inflammatory cells were scattered throughout it.

In the intermuscular layer the exudation of leucocytes and endothelial cells was abundant. The ganglia as a whole were affected and presented in places a glassy, hyaline appearance with only an odd cell showing a nucleus, while the capsule was lined and surrounded by numerous leucocytes and endothelial cells. In one or two places an area of what appeared to be colloid was found where nerve cells would ordinarily be expected. The capillaries were congested and the endothelial cells were swollen. The most careful search for tubercle bacilli was in vain, but some Gram-positive diplococci, presumably pneumococci, were found (Fig. 3).

Discussion.

This is the eighth of a series of cases of cardiospasm which I have examined histologically, and all show lesions in the intermuscular area. The first three were examined for Dr. Brown Kelly, and the results were communicated by him in his Semon Memorial Lecture in 1926. The others will be reported in detail at another time. Meanwhile it is sufficient to note that some degree of fibrosis with degenerative changes in the nerve cells of Auerbach's plexus was present in all. Similar results have been reported by Hurst from examinations made by Rake and the late Adrian Stokes.

Until the case now under consideration was examined I was inclined to look upon the ganglionic changes as athero-sclerotic in origin, as the thickened blood vessels formed rather a characteristic feature of the sections, but the direct and indisputable evidence of bacterial invasion shown here makes a toxic basis for all the more credible, especially as the antecedent development of an acute febrile condition is not uncommonly reported in the literature of this disease.

In the normal act of swallowing the œsophagus is straightened out from its 'repose' position by the muscles of the tongue and hyoid bone. These

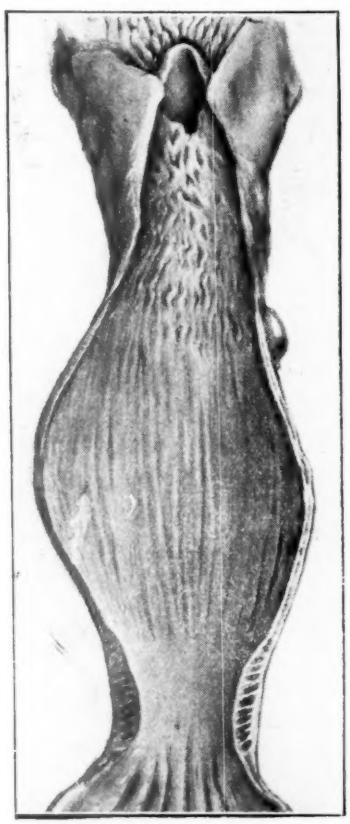

Fig. 1. Oesophagectasia. Child—6 years old.

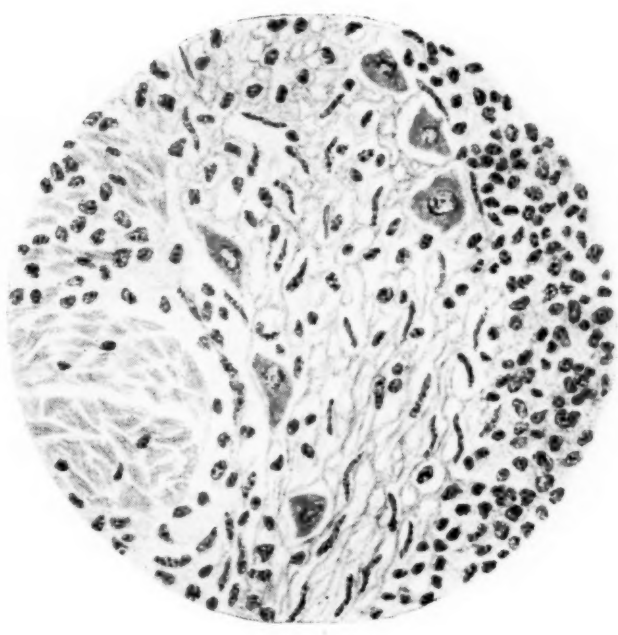

Fig. 2. High power drawing of section through cardiac canal, showing inflammatory exudate.

pull the larynx and cricoid plate away from the spine, and the inferior constrictor of the pharynx then starts the bolus on its course through the œsophagus. According to the researches of Kronecker and Meltzer the bolus at any point in its course causes contraction of the area just above it and relaxation below, the integrity of the cells in Auerbach's plexus governing this reaction. In a case such as I have described here the reflex is altered by the ganglionic changes and only contraction follows the stimulus. The retention of food slowly dilates the viscus and the circular muscle hypertrophies in an attempt to expel its contents. A striking feature of practically all recorded cases is the persistence of the hypertrophy throughout the dilated area; at times indeed, it appears to develop proportionately and *pari passu* with the enlargement.

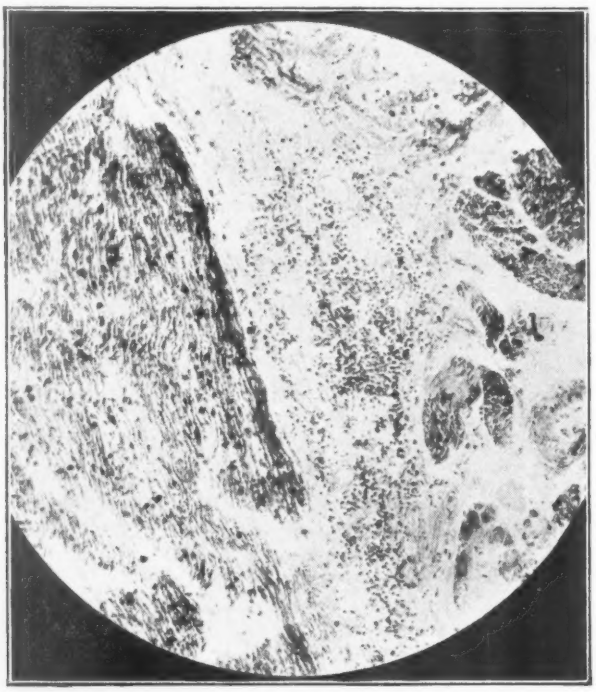

Fig. 3. Microphotograph showing degeneration of nerve cells with leucocytic exudation.

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HYPERTELORISM IN SEVERAL GENERATIONS.

BY

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Hypertelorism as defined by Greig in 1924 is a cranio-facial deformity of the sphenoid and nasal bones, often associated with mental deficiency and abnormalities of other parts of the skeletal and muscular systems.

The case which I am about to describe is in certain aspects peculiar, for in it there is no evidence of mental defect while there is good evidence of the inheritance of the cranial deformity through several generations. For the use of this case I am indebted to Mr. Dodds Parker, to whom the boy was brought on account of an inguinal hernia.

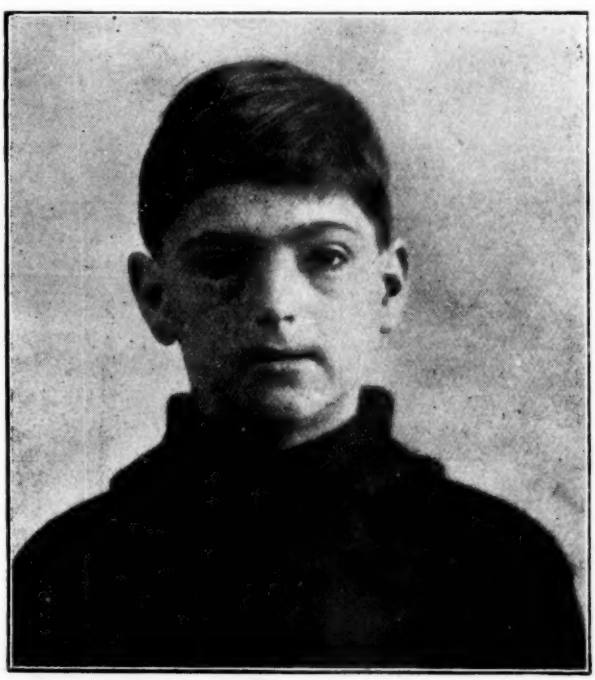

Fig. 1. Boy, aged 10, showing hyperteloric facies.

Fig. 2. Patient's mother and baby sister.

Fig. 3. Patient's maternal uncle.

Fig. 4. Patient's maternal uncle as a baby.

Case Record.

T. M. (Fig. 1), a boy aged 10 years was admitted to the Radcliffe Infirmary for the cure of a right inguinal hernia. On examination he was found to show the typical signs of hypertelorism.

He is the eldest of six children; the other five are all girls, the eldest of whom is 8 years of age. Of these one only, the youngest, shows a similar abnormality.

The *family history* is of distinct interest as the maternal grandfather, the mother and the mother's brother were all recognized by their friends as having their eyes abnormally widely spaced. This is quite noticeable in the photographs of the mother (Fig. 2), who is shown with the youngest baby, and in that of her brother (Figs. 3 and 4), but the photograph of the grandfather showed but little abnormality. There is no history of any cranial abnormality in the father's family.

The pregnancy ran a normal course: the child was breast-fed for five months. He had measles at 18 months and mumps at 4 years of age, but no other illnesses.

The peculiar breadth between the eyes was noticed in early infancy and was attributed to inheritance from the mother's family. The parents are not blood-relations.

General condition is excellent. The skin is soft and healthy: the subcutaneous fat is not abnormal in amount or distribution. His muscular development is good: he is a "Wolf-cub" and plays the ordinary games of boys of his age.

Mental Condition. The child seems to be remarkably intelligent: he attends school and is in Standard IV in which the average age of the boys is about 10 years. He finds his school work neither particularly easy nor too hard. He is interested in locomotives and knows the names and the functions of their various parts. He draws very well, much better than most boys of his age.

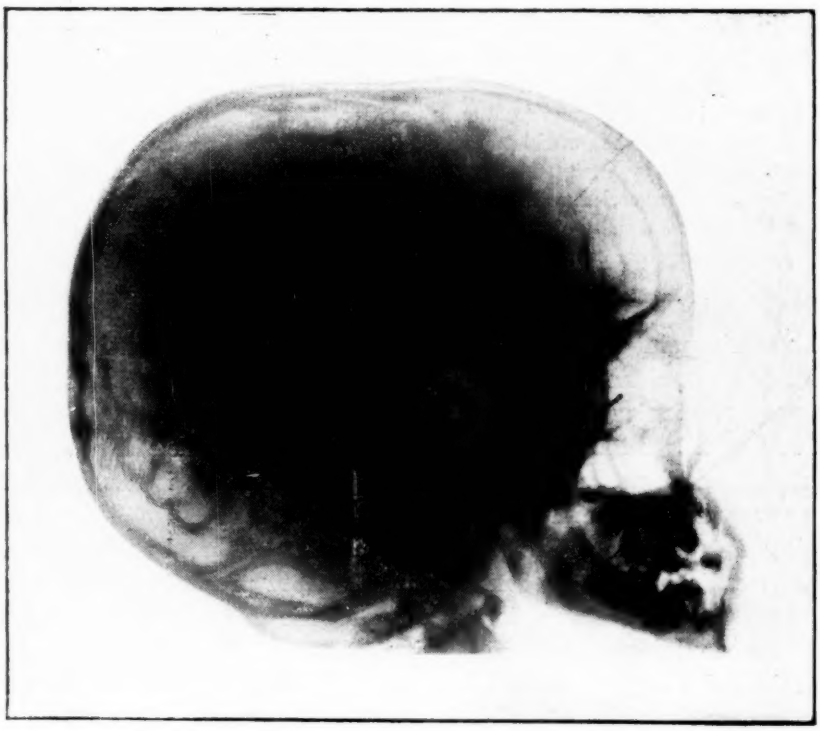

Fig. 5. Skiagram of patient's skull

Physical Examination. Age 10 years, height 133·1 cm. The skull is somewhat square, and broader behind than in front, the greatest breadth being the bi-parietal, 147 mm. The forehead is broad and approximates to the vertical. The upper facial index is 46, the lower 77. The occiput is broad and steep and the lambda rather high. The glabello-occipital length is 179 mm. and the minimum frontal diameter 105 mm.

The fundi oculorum are normal. There is slight ptosis of the upper lids of both eyes, slight nystagmus and external strabismus. Binocular vision is present. The external ocular breadth is 87 mm. and the internal 47 mm., the intra-orbital width is 19 mm., the external orbital breadth is 99 mm.

The ears are normal in shape and lie close to the head. The bridge of the nose is broad and flat but the organ is well shaped below, the nostrils being small and regular in outline. The nasal height is 40 mm., nasal length 35 mm., and breadth 27 mm. There is no nasal obstruction. The inter-zygomatic breadth is 124 mm. and the inter-malar 96 mm. The upper face length is 57 mm., and the total face length 95 mm. The nasal index is 67 and the cephalic index 82.

The tongue is normal in size, shape and activity. Of the teeth, four sound permanent incisors are present above and below, the permanent canines are erupted in the lower jaw. The first pre-molar is present on both sides in the upper jaw. All the remaining milk teeth are carious in some degree. The palate is narrow and highly arched: the tonsils show no abnormality. There are no enlarged lymphatic glands nor other abnormality in the neck. The heart and lungs are normal. In the abdomen the only abnormality is the presence of a right inguinal hernia, congenital and reducible, with a small hydrocele of the tunica vaginalis of that side. There is no hernia nor protuberance of the umbilicus which lies mid-way between the pubic symphysis and the xiphisternum. There is no phimosis, and both testes are in the scrotum. The arms and legs are well formed, symmetrical and muscular. The fingers are normal in shape, neither stumpy nor thickened, though the hands are somewhat broad. Both feet show a minor degree of pes cavus, and both great toes are rather unusually far distant from the second digits. There is a very slight webbing of all the toes but no sign of this in the hands. X-ray photographs of the hands and feet show no such abnormalities as were found in Greig's and Cockayne's cases, the broadness of the hands being accounted for by the soft parts. The tendon reflexes in the arms are brisk, those in the legs normal, except for the knee-jerks which are sluggish. The plantar responses are flexor. Deep muscular pressure pain and tendon pressure pain are practically absent in the calves. The Sigma reaction is negative. The X-ray photograph (Fig. 5) of the skull corresponds with what would be expected from the cranial measurements, but the bony deformities described by Greig and recognised as characteristic of the condition are present, if at all, in a minor degree. The short broad nasal bones, however, the massive sella turcica and the unusual size and density of the lesser wings of the sphenoid are sufficiently definite in this case to put the diagnosis beyond doubt.

Discussion.

The main point of interest in this case lies in the apparently indisputable hereditary transmission of the deformity through three generations of both sexes, unaccompanied by stigmata of mental deficiency.

Further, this child and his hypertelorie maternal uncle share a fondness for and a marked proficiency in draughtmanship, which is not found in any of the other ateloric members of the family.

While it is possible, as Greig suggests, that the advanced cases of the disease are the sporadic results of degeneracy in the stock producing them, there are no obvious grounds for applying that hypothesis to these milder cases which present no mental or physical infirmity.

Braithwaite suggests that the sphenoidal deformity may in mongolism be either the cause or the result of dyspituitarism, and further that a lesion of the pituitary gland may be a factor common to hypertelorism and mongolism.

In the case under review there is no evidence of any functional pituitary lesion, although marked sphenoidal deformity is present.

The present case, though it throws no light upon the causes of mongolism, clearly shows that dyspituitarism is no necessary consequence of sphenoidal deformity: it suggests rather that hypertelorism and mongolism are probably not inter-related, the former being perhaps primarily of endocrine origin, the latter a somatic deformity.

The justifiable inference seems to be that in these cases we are dealing with a Mendelian "sport" which, as it is not sufficiently removed from the normal to impair the efficiency of the organism has, like the majority of such sports become fixed, and so a normally hereditable Mendelian asset. For obvious reasons the grosser examples of the malformation fail to be propagated: these may be the results of racial degeneracy which is, perhaps, the most obvious factor in the production of mentally and physically abnormal individuals.

At the same time abnormal members do occur in the soundest stocks, and it is possible that the shape of the sphenoid, like the number of digits, may be developmentally one of the "weak spots" which, although normally fixed, are more liable to extra-normal variations, whether advantageous or disadvantageous to their possessors, than the other members of the body.

I wish to thank Mr. Dodds Parker for permission to publish this case, and Sir Archibald Garrod for his kindness in putting at my service the literature of the previously recorded cases. I am indebted to Mr. Dudley Buxton for his anthropometric study of the boy's head and other measurements, and to Dr. Sankey for the taking and reproduction of the X-ray photographs.

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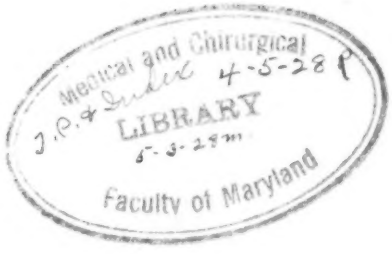
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